The New England
Journal of Medicine

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Volume 255 JULY 19, 1956 Number 3

METALLOENZYMES AND MYOCARDIAL INFARCTION*

I. The Relation between Serum Copper and Ceruloplasmin and Its Catalytic Activity

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ALTHOUGH 90 per cent or more of the copper content of normal human blood serum can be accounted for by the metalloenzyme, ceruloplasmin, few studies concerning the variability of this protein with changes in serum copper concentration are available. Variation of serum oxidase activity in proportion to the copper content has been shown in leukemia and polyarthritis and in the neonatal period.[1] Enzymatic and immunologic technics indicate the existence of a linear relation between the serum copper and ceruloplasmin and oxidase activity in pregnancy, infection and the nephrotic syndrome.[2] In Wilson's disease, a disproportionate decrease of serum copper concentration and of ceruloplasmin content has been demonstrated.[3]

The serum copper concentration is elevated in many acute and chronic pathologic states.[4,5] A report from this laboratory[6] has shown a persistent elevation after acute myocardial infarction. This change ordinarily begins on the second or third day after infarction, continues to a maximum elevation on the fifth to the eleventh day and gradually decreases to normal within several weeks. In pregnancy, the serum copper level rises gradually beginning in the eighth week, continues to a maximum in the thirty-second and thirty-fourth weeks and returns to normal in the sixth to the tenth week post partum.[7,8] Eighty-nine per cent of normal serum copper and 93 per cent of pregnancy serum copper are precipitated by 26.8 per cent sodium sulfate.[9] These findings have been substantiated by others.[10,11]

The simultaneous study of the copper concentration, the ceruloplasmin content and the enzymatic activity of serum would provide information concerning the origin of an elevated copper content if a disproportionation between these parameters could be detected. It is desirable, furthermore, to establish the precise relations between the enzyme content and elevated serum copper levels. In the present study serum was obtained from normal donors and from two groups, representing the *rapid* and the *gradual* time course of serum copper elevation: patients with acute myocardial infarction and pregnant women.

Investigations of the physical chemistry of ceruloplasmin prove it to be a metalloprotein containing 0.34 per cent copper, with a specific absorption maximum at 605 millimicrons attributable to the copper-protein complex, and capable of acting as an oxidase toward a number of substrates, including several polyphenols, ascorbic acid, paraphenylenediamide and benzidine.[11]

MATERIALS AND METHODS

Serum was obtained from 10 normal subjects between the ages of eighteen and thirty-four, of whom 4 were female and 6 male, 18 women between the ages of eighteen and thirty in the second and third trimester of pregnancy, and 6 male and 2 female patients between the ages of fifty-five and seventy with proved recent infarction of the myocardium. Electrocardiographic changes, as well as the clinical and laboratory course, were employed as criteria for the existence of an infarction. Each patient was sampled two to eight times during the three weeks after admission. The serum copper concentration had to exceed 155 microgm. per 100 ml. at some time during this period to make the patient under study eligible for inclusion in this series. The range of normal serum copper concentration was taken as 80 to 140 microgm. per 100 ml.[6]

All samples were collected in metal-free, acid-cleaned syringes through special stainless-steel

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Supported by a contract between the Office of Naval Research and Harvard Medical School (Contract No. NR 119-277) and by the Howard Hughes Foundation for Medical Research.

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needles,* and most were taken three hours or more after meals, although no variation in serum copper has been noted during the daytime or after meals.[6] Metal-free, acid-cleaned glassware was used throughout. Serum was separated from the cells one hour after collection, stored in the cold at 4°C. and analyzed within ten days for copper and ceruloplasmin content and the capacity to oxidize paraphenylenediamine and benzidine.

TABLE 1. *Precision of Ceruloplasmin, Benzidine and Paraphenylenediamine Determinations.*

DETERMINATION	NO. OF DETERMINATIONS	MEAN	STANDARD DEVIATION	COEFFICIENT OF VARIATION
				%
Ceruloplasmin concentration (5-cm. trapezoidal quartz cell, optical density measured at 610 millimicrons)	14	0.071	±0.007	±10.0
Benzidine oxidation (1-cm. cell, optical density measured at 600 millimicrons)	13	0.235	±0.006	± 2.4
Paraphenylenediamine oxidation (measured as microliters oxygen per hr.)	15	44.0	±2.1	± 4.7

Serum Copper Concentration

The concentration was measured spectrophotometrically by means of the copper diethyldithiocarbamate method.[6,12]

Enzymatic Activity

This was measured in two ways:

Capacity to oxidize paraphenylenediamine was determined gasometrically.[1] To 0.6 ml. of sodium acetate-acetic acid buffer (0.15-molar solution, at pH 6.0), in a Warburg flask, 0.3 ml. of serum was added, having previously been dialyzed for twenty-four hours at 4°C. against the same acetate buffer. After thermal equilibrium had been attained at 37°C., 1.0 ml. of a solution containing 5 mg. of paraphenylenediamine per milliliter was tipped in from the side arm, and the oxygen consumption was measured in a standard Warburg respirometer. Readings were taken every ten minutes for seventy minutes, and the *rate* of oxygen consumption was calculated. The correction for the auto-oxidation of paraphenylenediamine was determined by measurement of the rate of oxygen consumption of the same volume of substrate and buffer in the absence of serum.

Capacity to oxidize benzidine was determined spectrophotometrically.[2] Serum was diluted with an equal volume of 0.05-molar Veronal buffer (at pH 7.2) in 0.1-molar sodium chloride, and 2.0 ml. of this mixture was then added to 2.0 ml. of the same buffer mixture (at pH 7.2), containing a standard concentration of benzidine. The buffered benzidine solution was standardized in the following manner: 0.1 gm. of benzidine dihydrochloride was taken up to 25 ml. in the Veronal-sodium-chloride buffer. The pH of the mixture was adjusted to 7.2 with potassium hydroxide. After mixing for forty minutes at 37°C., the solution was filtered quickly through Whatman No. 41 filter paper and kept at 37°C.; 1 ml. of this clear solution was then diluted with water to 100 ml., and the optical density of the diluted aqueous solution determined in a 1-cm. quartz cell at 300 millimicrons. The dilution of the original, concentrated benzidine solution with Veronal buffer was then adjusted, so that 1.0 ml. diluted to 100 ml. had an optical density of 0.300.

Samples were incubated for sixteen hours at 37°C. After centrifugation at 3,000 rpm for fifteen minutes, the supernatant fluid was decanted into a 1-cm. Beckman cell, and the optical density determined at 600 millimicrons. A control containing 2.0 ml. of diluted serum combined with 2.0 ml. of Veronal buffer alone was also incubated and used as the reference solution for spectrophotometric measurement.

TABLE 2. *Effect of Two Weeks' Storage at 4°C. on Copper Content, Ceruloplasmin Content and Paraphenylenediamine and Benzidine Oxidation of Human Serum.*

INTERVAL AFTER PHLEBOTOMY	COPPER	CERULOPLASMIN CONTENT*	BENZIDINE OXIDATION†	PARAPHENYLENEDIAMINE OXIDATION
days	*microgm./100 ml.*			*microliters/hr.*
1	129	0.041	0.260	51
	131	0.036	0.266	41
3	139	0.039	0.275	48
	127	0.032	0.273	48
7	135	——	0.284	41
	131	——	0.289	41
14	132	0.038	0.298	—
	138	0.032	0.301	48
Coefficient of variation	(3.2%)	(10.3%)	(6.3%)	(9.5%)

*5-cm. trapezoidal quartz cell, optical density measured at 610 millimicrons.
†1-cm. cell, optical density measured at 600 millimicrons.

Ceruloplasmin content. Carbon dioxide was bubbled through 3.0 ml. of serum for one minute; 0.5 ml. of 0.85-molar sodium chloride was added to 2.5 ml. of the carbon dioxide saturated serum, and the mixture transferred to a 5-cm. trapezoidal quartz cell similar to those elsewhere described,[13] and the optical density determined at 610 millimicrons with the use of distilled water as reference solution. Then, 0.1 ml. of 1.5-molar potassium cyanide adjusted to pH 7.8 with hydrochloric acid was added to the sample, and the optical density recorded every fifteen minutes until a maximum decrease was achieved (usually, within thirty to forty-five minutes). The difference between the original and final reading was corrected for changes in volume, and determined the ceruloplasmin concentration.

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Results

The precision of the several methods (capacity to oxidize paraphenylenediamine and benzidine, and ceruloplasmin content) was determined. These data are summarized in Table 1. The coefficients of variation were as follows: ±4.7 per cent for the paraphenylenediamine oxidation method; ± 2.4 per cent for the benzidine oxidation method; and ± 10 per cent for the method determining ceruloplasmin concentration. The precision of the method for serum copper had already been established as 2 or 3 per cent.[13]

Since determinations were performed up to ten days after phlebotomy (and the separation of serum from the formed elements), duplicate analyses of the same serum, stored at 4°C. for one, three, seven and fourteen days after collection, were made (Table 2). The coefficients of variation were as follows: paraphenylenediamine oxidation, 8.5 per cent; benzidine oxidation, 6.3 per cent; ceruloplasmin concentration, 10.3 per cent; and serum copper concentration, 3.2 per cent.

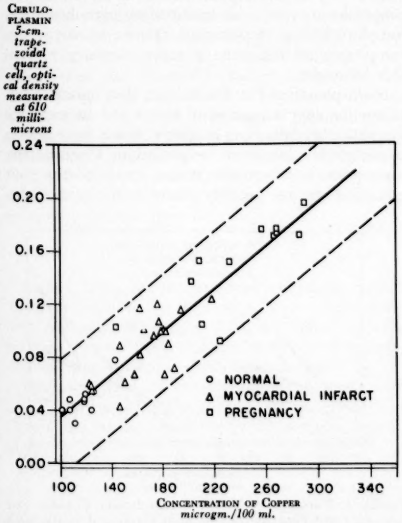

FIGURE 1. *Variation of Serum Ceruloplasmin Content (As Measured by Potassium Cyanide Decolorization), with Copper Concentration.*

The results of all determinations are presented graphically in Figures 1-3. Ceruloplasmin content, paraphenylene oxidation and benzidine oxidation, respectively, are plotted against serum copper concentration. Normal and pregnant subjects and patients with acute myocardial infarction are represented and differentiated similarly in each graph. In addition, the best line and limits of the range are shown. The correlation coefficients for these grouped data are: 0.87 for the ceruloplasmin and 0.92 for the paraphenylenediamine oxidation vs. copper concentration. For benzidine oxidation vs. copper (Fig. 3), a marked discrepancy is apparent between the distribution of values for the data points representing the myocardial-infarction group, on one hand, and the regression line, which can be drawn through the origin and the points representing serums from normal and pregnant subjects. The correlation coefficient calculated for the last two groups alone is 0.90.

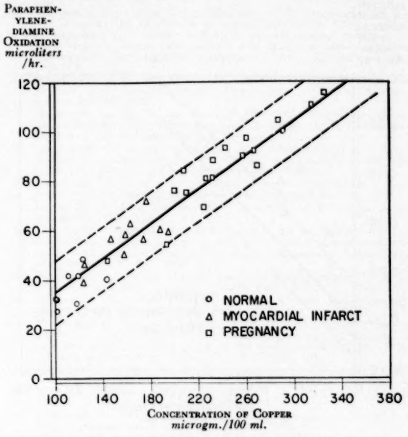

FIGURE 2. *Variation of Serum Paraphenylenediamine Oxidase Activity, with Copper Concentration.*

In Figure 4, three consecutive values of serum benzidine, paraphenylenediamine oxidation and ceruloplasmin content as a function of copper content are shown for 2 patients after acute infarction of the myocardium. Paraphenylenediamine oxidation and ceruloplasmin values lie along a common line in both cases whereas the disproportionate increase of benzidine oxidation over that of the copper concentration is well demonstrated by an abnormal rise in the benzidine value on the seventh hospital day.

Discussion

Copper concentration, ceruloplasmin and its enzymatic activity have been measured by four independent methods. The precision of three of the methods is high and of comparable magnitude (Table 1).

The lowest precision is achieved with the determination of ceruloplasmin content by measurement of the decrease in the optical absorption at 600 millimicrons in the presence of cyanide. This is to be expected, since the method depends upon the reduction

of an absorption maximum due to a single, minor constituent of serum, which is a heterogeneous mixture of macromolecules. This provides high background and considerable light scattering because of the inhomogeneity of the samples. We have attempted to minimize this effect by filtering serum through scintered glass, but without appreciable improvement in precision.

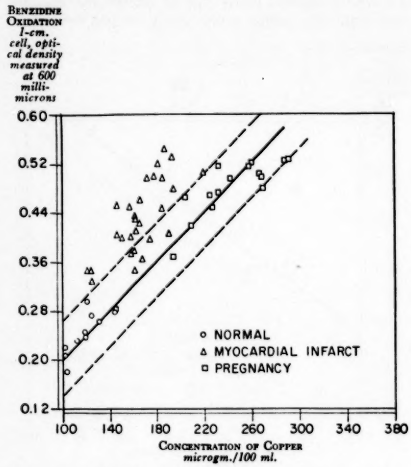

FIGURE 3. *Variation of Serum Benzidine Oxidase Activity, with Copper Concentration.*

Since many copper-protein complexes absorb light in the region of 600 millimicrons,[14] ceruloplasmin is uniquely determined by this method only if the concentration of other copper proteins in the serum is negligible. The difference spectrums of serum and purified ceruloplasmin before and after the addition of cyanide have been examined and found to be identical over the wave-length region of 450 to 800 millimicrons. The failure of the regression line relating the optical-density change at 610 millimicrons and serum copper concentration to pass through the origin is apparent. An analysis of the technic leads us to believe that this failure to pass through the origin is an artifact of the method and does not represent nonceruloplasmin, nonabsorbing copper. The extinction coefficient calculated for the slope of the curve shown and corrected for dilution compares favorably with the published value of the extinction of pure ceruloplasmin.

Ascorbic acid and sodium hydrosulfite can also be employed to decrease the absorbency at 610 millimicrons. Cyanide is the preferred agent, for the reduction by the other compounds is readily reversed by oxygen and must be carried out in an inert atmosphere.

High precision for the benzidine method was achieved by standardization of the benzidine concentration to constant absorbency at 300 millimicrons. This spectrophotometric method is more convenient and precise than the gasometric determination of paraphenylenediamine oxidation employed in this study.

Serum copper concentration, ceruloplasmin content and paraphenylenediamine oxidation are linearly related throughout the concentration range studied, indicating that both the acute rise in serum copper that follows infarction of the myocardium and the slow rise during pregnancy can be accounted for by an increase in the serum ceruloplasmin content.

Though a linear relation also exists between serum copper content and capacity to oxidize benzidine for normal persons and pregnant women, the amount of benzidine oxidized by serum from patients with myocardial infarction is greater than can be accounted for by the copper increase alone. This disproportionate rise is not inhibited by pyrophosphate, but the addition of potassium cyanide to this serum completely inhibits the oxidative capacity toward this substrate.

No explanation for this striking disproportion between the copper content of serum and its capacity to oxidize benzidine can be given. Since the reaction is completely inhibited by potassium cyanide, the assumption is reasonable that a metal of the first transition group, possibly heme iron, is involved.

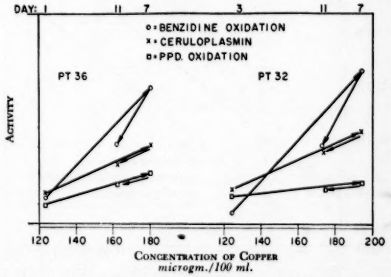

FIGURE 4. *Variation of Serum Ceruloplasmin Content and Benzidine and Paraphenylenediamine Oxidase Activity, with Copper Concentration, in 2 Patients after Acute Myocardial Infarction.*

Whether this increased activity to oxidize benzidine is due to the appearance of a new enzyme or to the increased *specific activity* of an existent serum enzyme remains to be demonstrated.

The correlation of rise in copper content with rise in ceruloplasmin content for myocardial infarction is consistent with the observation that in normal subjects an alpha$_2$-globulin fraction of serum contains a significant quantity of Cu^{64} twenty hours after administration of the isotope.[15,16] This is within

the period in which increased synthesis of ceruloplasmin, a constituent of the globulin fraction of serum, might take place after myocardial infarction.

The precise origin of this increased serum copper protein is unknown. Damage to the myocardium alone after infarction cannot explain it, since the extent of the copper elevation during this period is greater than can be accounted for by the cardiac copper content. One possibility is the release of the metalloprotein or its precursors from stores elsewhere, since copper has an ubiquitous distribution in the body.[5] At present, little is known of the natural state of copper in these stores. Of the other isolated copper proteins, ceruloplasmin most closely resembles the hemocuprein,[17] which has one fourth the molecular weight and copper content, but none of the enzymatic properties of the serum oxidase. An increased synthesis, or decreased breakdown, of the protein, possibly by the liver, can be postulated and tested for experimentally as a hypothesis to explain this increase.

Factors regulating the serum copper protein levels are also unknown. The physiologic rise accompanying pregnancy suggests a hormonal influence consistent with the peculiar endocrine balance of this state. Regarding adrenocortical influences, the administration of ACTH restores the hypercupremia of leukemic patients toward normal.[18] Melanocyte-stimulating hormone does not appear to influence the serum copper concentration.[19] A relation between serum copper levels and thyroid activity has been suggested, but not proved.[20]

Summary

Serum from normal subjects, pregnant women and patients suffering from acute myocardial infarction was analyzed for total serum copper concentration, ceruloplasmin content and paraphenylenediamine and benzidine oxidative capacity.

Benzidine oxidase was elevated in patients with acute myocardial infarction to an extent greater than could be accounted for by the copper elevation alone.

A linear relation between copper concentration, ceruloplasmin content and paraphenylenediamine oxidation was found for all three groups.

We are indebted to Drs. Duncan E. Reid and James Metcalfe and the staff of the Pre-Natal Clinic of the Boston Lying-in Hospital for co-operation and to Miss Martha Quinn for technical assistance.

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PROBLEMS IN ANESTHESIA FOR OPERATIONS ON THE HEART*

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IMPROVEMENTS in anesthetic technics have contributed in large part to the advance of cardiac surgery. On the other hand cardiac surgery has progressed so rapidly in the last decade that anesthesia has been hard pressed to keep abreast of the problems presented. Perhaps because of increased knowledge of the physiology of heart disease and the pharmacology of anesthetic agents, the reported results of anesthesia for cardiac surgery have been relatively good.[1-3] In this clinic a great deal of surgery is accomplished in poor-risk patients, with excellent results. It is the purpose of this report, however, to review some of the difficulties encountered and the mistakes made in the anesthetization of patients with acquired heart disease who are extremely poor risks. This experience extends over a period of years, during which many anesthetic agents and technics have been employed. The work has been done in an academic department under continued close supervision.§

The changing pattern of cardiac surgery provides the background for this paper. Poorer and poorer risks have been brought into the orbit of surgery. Various technics have been directed at the correction of mitral stenosis, mitral insufficiency, aortic stenosis and aortic insufficiency. Few procedures have stood the test of time, because of prohibitive mortality or equivocal results. Generally, experimental procedures have been offered the near-moribund patient in attempts at salvage. Mitral valvuloplasty for stenosis has been the most successful operation. Yet the operative mortality is still in the range of 20 per cent for Group 4 patients, the terminal group.[4] These are persons in whom the duration and degree of stenosis have progressed beyond mere pulmonary arterial hypertension to intractable congestive heart failure. Advancing age, calcification of the mitral valve, atrial fibrillation and systemic embolization add to the risk of anesthesia and operation. In another sphere, when syncope, angina or failure of the left ventricle develops in a patient with aortic stenosis the prognosis is grave.[5] These are examples of patients who must be anesthetized for heart surgery. The untoward effects of all anesthetics are exaggerated here. It is easy to ascribe complications and death to the preexisting disease if the subtle effects of anesthetics are not scrutinized. We have therefore selected typical cases to illustrate some of the complications of anesthesia and to suggest the means of prevention.

PREOPERATIVE PREPARATION AND CHOICE OF PREANESTHETIC MEDICATION

Digitalis, Body Fluids and Electrolyte Balance

The procedures and drugs used to prepare patients for heart surgery often, in themselves, add to the problems of anesthesia. It is an established regimen to prepare patients for operation by digitalization and to reduce congestion in heart failure with diuretics, restriction of salt and fluids.[6] In rigorous treatment directed at a dry body weight, disturbances in body fluids and electrolytes may ensue.[7] Hyponatremia, hyperkaliemia and increases in the volume of extracellular fluid are perpetuated by the ordinary endocrine and metabolic responses to operation. The important effects of these changes on the response of the heart and circulation to anesthetics need further elucidation. Digitalization per se is not always a clear end point. It is a matter of real importance to decide before anesthesia is begun if the patient is properly digitalized. Overdigitalization is more commonly seen, but the classic signs of toxicity may be absent. This, coupled with already present electrolyte disturbance, can account for some difficulties described below. We believe that some of the ventricular tachycardia and the conduction defects encountered during anesthesia may be related to a combined digitalis-anesthetic effect. Cases 1 and 2 illustrate aspects of this problem.

CASE 1. T.F. (P.B.B.H. 9G9), a 63-year-old man, was admitted to the hospital with intractable heart failure secondary to aortic stenosis. Five years before, after an attack of squeezing chest pain, he was found to have a coronary-artery occlusion. At the age of 61 generalized anasarca was followed by increasing fatigue and complete inactivity just before entry. Physical examination showed a cachectic man with hepatomegaly and peripheral edema. The heart extended beyond the midclavicular line. A rough systolic murmur was heard over most of the precordium. There was normal sinus rhythm, and the blood pressure was 98/65. An electrocardiogram showed hypertrophy of the left ventricle and probably an old anterior septal infarction. A roentgenogram revealed a calcified aortic valve and coronary-artery calcification. Simultaneous catheterization of the left and right sides of the heart confirmed the diagnoses of left-sided failure and aortic stenosis. He was prepared for a transaortic valvuloplasty, but operation had to be postponed repeatedly because of the appearance of atrial premature beats and bigeminal rhythm. Digitalis was discontinued, and 5 days later a provocative acetyl-strophanthidin test showed persisting digitalis toxicity. It was only after 19 days without digitalis that it was considered safe to proceed with anesthesia and operation.

CASE 2. J. A. (P.B.B.H. 9G637), a 32-year-old married woman, had frank aortic insufficiency. There was a history

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§Practically all the cardiac surgery has been performed by Dr. Dwight E. Harken and the thoracic group. We are indebted to them for the experience we have had and for their help and criticism.

of many sore throats, chorea and a heart murmur. Over a period of 8 years increasing fatigue, dyspnea and orthopnea finally caused her admission to the hospital. Frank cardiac decompensation had not occurred, and she had never been given digitalis. Examination revealed a heart whose border extended beyond the midclavicular line. Grade 3 systolic and Grade 4 diastolic murmurs were heard over the aortic area. The blood pressure was 180/40. The peripheral pulses exhibited pistol-shot sounds and Duroziez's sign. She was digitalized on entry and prepared for the insertion of a prosthetic aortic valve for aortic insufficiency. Operation was delayed because of a prolonged upstroke time in the brachial-artery pulse, suggesting failure of the left ventricle. Several days later, during induction of anesthesia with thiopental, nitrous oxide and ether, ventricular premature contractions and ventricular tachycardia arose. Operation was cancelled but successfully completed 2 weeks later.

In Case 1 it is likely that difficulty would have arisen during operation if an anesthetic had been given in the presence of digitalis toxicity. In Case 2, although one cannot eliminate the effect of the anesthetics and concomitant hypoxia, one wonders about the role of digitalis. Thus, one must determine in the immediate preoperative period if a tachycardia indicates apprehension, under digitalization, or digitalis toxicity. An electrocardiogram should be taken just before administration of anesthesia and compared with the earlier recordings. It is pointed out below that the electrocardiograph is an important monitoring device during operation. Tachycardia due to apprehension sometimes disappears with added sedation, or after induction of anesthesia. Rarely, tachycardia concurrent with active rheumatic carditis will not be amenable to any therapy. In any case a rapid heart rate may lead to pulmonary edema, hypotension, myocardial failure or ventricular fibrillation. In analyzing our records we find preoperative tachycardia to be associated with a higher postoperative mortality.

Preoperative Medication

For many years it has been standard practice in anesthesia to give an opiate and atropine before operation. It was held that the opiates would provide sedation and euphoria and lessen the amount of general anesthetic needed. Atropine would block mucous secretion and protect the heart against vagal impulses. Re-examination of these concepts has shown that few of these objectives are actually achieved. The opiates at least do more harm than good. Thus, the choice of the safest preoperative medication is a matter of balancing the possible ill effects of the patient's apprehension against the hazard of too much sedation. Most patients have painful apprehensions about leaving their rooms, much more the entrance to the operating room. Usually, a frank, reassuring discussion beforehand and the establishment of a good patient-anesthetist relation will obviate this problem. Morphine or meperidine (Demerol) more often leads to circulatory instability rather than desirable euphoria. One may accentuate the hypotensive action of any of the opiates by transferring the patient to the operating theater and the subsequent use of potentially hypotensive anesthetic agents. Some patients with mitral stenosis may tolerate hypotension, but it can be disastrous in aortic stenosis or coronary insufficiency. In Cases 3 and 4 morphine and its combination with anesthesia forced cancellation of operation. It is probably true that the relatively fixed stroke volume of advanced stenosis and the peripheral vasodilatation of general anesthesia added to the hypotension in Case 3.

Case 3. G. A. (P.B.B.H. 3G648), a 42-year-old woman, had had a known heart murmur of mitral stenosis since the age of 16 and several subsequent attacks of acute rheumatic fever. She had been started on digitalis 6 years before admission after a bout of pulmonary edema. Attacks of acute congestion followed, as well as a cerebrovascular accident on the right 3 years before entry. On admission to the hospital the heart was enlarged, with a Grade 2 diastolic murmur heard at the apex. The blood pressure was 126/80. An electrocardiogram revealed atrial fibrillation and hypertrophy of the right ventricle. A roentgenogram showed calcification of the mitral valve. Mitral valvuloplasty was scheduled; 100 mg. of pentobarbital (Nembutal) and 10 mg. of morphine were given as preoperative medication. The blood pressure immediately before operation was 70/50. After induction of anesthesia with thiopental, nitrous oxide, ether and curare the patient was turned on her side. At this point the blood pressure could not be obtained, and operation was canceled.

Operation is not always canceled when arterial hypotension is seen during induction of anesthesia and positioning of the patient. Vasopressor drugs can be given, and the outcome awaited. However, with the poorer risks and especially when the peripheral blood pressure cannot be heard, it is wiser to perform the operation at another time under better circumstances.

Case 4. W.P. (P.B.B.H. 5G197), a 52-year-old man with aortic stenosis and insufficiency, first noted fatigue at the age of 47. This progressed until congestive heart failure, bouts of paroxysmal nocturnal dyspnea and a periodic sensation of substernal constriction in the chest developed. On admission he was thin, pale, sweating and orthopneic. Grade 4 systolic and Grade 2 diastolic murmurs were heard in the aortic area. The blood pressure was 85/50. The pulse was regular, and the liver edge was felt 2 fingerbreadths below the right costal margin. Fluoroscopy revealed calcification of the aortic valve. The upstroke time of the brachial-artery pulse lasted 0.22 second, or twice the predicted normal of 0.11 second. With a diagnosis of calcific aortic stenosis aortic valvuloplasty was scheduled. For preoperative medication he was given 100 mg. of pentobarbital and 10 mg. of morphine. On arrival in the operating room the blood pressure could not be obtained by auscultation. When the same preoperative medication was given on the ward several days after cancellation of operation the result was the same. A week later, with half the original preoperative medication, the blood pressure again disappeared when he was placed on his side. Induction of anesthesia had been performed with thiopental, ether and curare and a respiratory assistor was used.

It seems fairly clear that hypotension in Case 3 resulted from a combination of pharmacologic effects whereas in Case 4, a direct relation to morphine was established. Many cardiac patients after anesthetization become hypotensive when placed in the lateral

position for operation. Wood and Wolferth[8] have described a phenomenon of trepopnea in patients with heart disease when there is a change of recumbent position although there is no accompanying blood-pressure alteration. It seems wise not to place an anesthetized patient in a position he could not tolerate when awake. The lesson is that opiates should be avoided or given sparingly if the planned anesthetic technic requires their use. Beecher[9] has pointed out that the barbiturates though potentially hypotensive are satisfactory and safer for preoperative medication and the management of apprehension. The so-called tranquilizing drugs, chlorpromazine and reserpine, seem unsafe in the preoperative period because they too may produce the hypotension that we try to avoid.

Atropine or its substitutes are not given routinely for preoperative preparation. Usually, secretions are minimal or absent with the small concentrations of general anesthetic given. Larger amounts of atropine, in the range of 1 mg., which still only partially block vagal stimuli, provide a hazard in tachycardia, particularly in the digitalized patient with a satisfactory ventricular rate. There is also a tendency for changes in rate and rhythm to appear in the digitalized patient when meperidine is employed. Because of the muscarinic effect of meperidine some have avoided its use in heart disease, particularly atrial flutter.[10]

Induction of Anesthesia

Induction of anesthesia well may be the most hazardous phase of the operation. During this period any difficulty in anesthetic management or unusual response of the patient may lead to excitement, cough, breath holding, hypoxia or overdosage with the anesthetic agent. This series of events is seen often during induction with inhalational agents. The following case, with a fatal outcome, demonstrates the effect of unexpected stress on a damaged myocardium with a limited coronary-artery blood flow.

Case 5. E. G. (P.B.B.H. 9G350), a 37-year-old man with aortic insufficiency, first noticed dyspnea on exertion at the age of 25. Subsequently, there were attacks of arthritis and acute rheumatic fever. At 35 he began to have typical anginal attacks precipitated by exposure to cold and exertion and relieved by nitroglycerin. For 1 year he had had dyspnea at rest, hemoptysis, ascites, ankle edema and paroxysmal nocturnal dyspnea. When examined he was found to be surprisingly well nourished and well developed. The heart was enormous, extending virtually from axilla to axilla. Systolic and diastolic murmurs were heard in the aortic area, accompanied by a systolic thrill. The blood pressure was 244/0. The aortic valve was calcified on the roentgenogram, and the electrocardiogram exhibited hypertrophy of the left ventricle. Preparations were made for insertion of a prosthetic aortic valve for the aortic insufficiency. Induction of anesthesia with a small amount of thiopental given intravenously followed by ether brought on coughing, breath holding and cyanosis that could not be overcome. The heart ceased to beat within a few minutes and could not be resuscitated though the chest was opened promptly.

An experience of this sort emphasizes the fact that the surgeon must be present during induction of anesthesia in the event that thoracotomy and manual restoration of systole are indicated. This death was due to a combination of circumstances that, though commonly seen, are of little consequence in the good-risk patient. Although the intent was to induce anesthesia quickly and with little stress, the resultant coughing and Valsalva effect, with decrease in cardiac output and hypoxia, were too much for this patient's myocardium. The same sequence of events might have taken place if attempts had been made to intubate the trachea under topical anesthesia with the patient awake, or if an irritating inhalational anesthetic had been given at the beginning. The hemodynamic effects of the Valsalva maneuver consequent to breath holding and cough differ in the anesthetized patient in comparison to those of a normal subject. The compensatory sympathetic-nervous-system response may be obtunded in the former and the more so with increasing depth of anesthesia.[11] The anesthetic agent employed may also alter the response.[12] On the other hand patients with an increase in central venous pressure may not exhibit a fall in blood pressure at all.[13] This may explain why some patients with congestive heart failure, mitral stenosis and constrictive pericarditis tolerate stormy induction of anesthesia. Nevertheless, hypoxia associated with breath holding may lead to sudden death. A similar mechanism at a different time is illustrated in the following unfortunate but instructive case of performance of postoperative tracheal toilet.

Case 6. A. H. (P.B.B.H. 9G373), a 40-year-old man, had a history of active rheumatic fever at 13, a heart murmur of mitral stenosis discovered at 17, and the onset of dyspnea on exertion at 35 years of age. His body weight, which had been 113.4 kg. (250 pounds) had fallen to 63.5 kg. (140 pounds) in the last 2 years. He had had to sleep nearly upright for 2 years and had been bed ridden for 7 months because of anasarca. When examined he was found to be thin and cachectic, with bilateral pleural effusions, ascites and hepatomegaly. The cardiac border extended to the left axilla, and there were Grade 3 apical systolic, apical diastolic and Graham–Steell murmurs. The blood pressure was 125/85. Atrial fibrillation and hypertrophy of the right ventricle were confirmed by an electrocardiogram. According to Harken's classification of patients with mitral stenosis this man was in Group 4.[4] After a long period of preparation to correct electrolyte and protein deficiencies he underwent a successful mitral valvuloplasty under general anesthesia. On the evening of the 1st postoperative day at routine nasal catheter suction of the trachea, he coughed vigorously several times and died.

Stephenson, Reid and Hinton,[14] in a review of cardiac arrest associated with anesthesia, found that many arrests occurred with tracheal manipulation during induction and emergence from anesthesia. Rather than a vagovagal response as suggested by these authors we believe that the prime factors may be hypoxia and hypotension. For this reason we seldom perform routine suction of the trachea during operations on the poor-risk patient and then only briefly when careful oxygenation of the lungs has been performed before and immediately after the

manipulation. The same technic should be followed during postoperative tracheal toilet.

Choice of Anesthetic Agent

Too often in the choice of anesthesia for problem cases attention is paid primarily to the theoretic benefits or hazards of one agent or technic. From the foregoing discussion it may have become apparent that no single agent or technic of anesthesia is suitable or safe for all types of cases. The crux of the matter is that the anesthetist must be versatile in several spheres and most of all familiar with his patient and the pathologic physiology of the disease. This accomplished, suitable agents and methods can be selected for the problem at hand. It has been shown that the mode of induction might have bearing on the difficulties encountered during anesthesia. Anesthesia has been induced in our poorest risks with simple inhalational methods, sometimes preceded by sedative doses of thiopental. Both nitrous oxide and cyclopropane can lead to a smooth and rapid induction. If, as the patient loses consciousness, the anesthetist talks, encourages and explains in a suggestive and indeed hypnotic manner, excitement is rare, and emergence from anesthesia is tranquil. Despite pharmacologic evidence in the dog that cyclopropane sensitizes the myocardium to injected epinephrine the utility of this gas in man is hard to exceed because of the rapidity of action, potency and controllability. Actually, the known vagal action of cyclopropane on the heart makes it useful in supraventricular tachycardia. If neostigmine is employed for tachycardia, why not a more controllable substance? In the following case, one of many, which is presented to illustrate these contentions, an anesthetic agent was given for the easy induction afforded the patient, in spite of theoretical objections to its use, and tachycardia was controlled at the same time.

Case 7. M. F. (P.B.B.H. 9G827), a 26-year-old man, had had many attacks of acute rheumatic fever. Subacute bacterial endocarditis 8 months before admission had been successfully treated. After a massive gastrointestinal hemorrhage he noticed greater dyspnea. Within 6 months of admission he had been digitalized because of atrial fibrillation and attacks of acute pulmonary edema. His appearance suggested thyrotoxicosis. The heart was greatly enlarged, with systolic and diastolic thrills and murmurs in the aortic area. The blood pressure was 170/45. Bacterial endocarditis again developed. The electrocardiograms consistently showed ventricular premature contractions and delayed conduction time. One month after admission he was sent to the operating room for insertion of a prosthetic aortic valve for aortic insufficiency. With a small amount of preoperative medication the pulse rate immediately before operation was 160 and supraventricular in origin. The rate was not altered with a trial induction of anesthesia, and the administration of 2 0.25-mg. injections of neostigmine. The operation was canceled. A week later the same situation prevailed despite doubling of the dose of preoperative medication. Anesthesia was then induced with cyclopropane, and the pulse rate reached normal levels. Operation was successfully concluded.

In short, maintenance of anesthesia for the poor-risk patient involves the lightest possible plane of narcosis consistent with amnesia and analgesia for the patient and good operating conditions for the surgeon. The most recent additions to the list of anesthetic agents — curare and the other muscle relaxants — have made this goal possible and added greatly to the safety of anesthesia for cardiac surgery. In some cases without the relaxants it is not possible to maintain a light plane of analgesia and to avoid the depressant effects of the inhalational agents on the myocardium. The shorter-acting relaxants allow for anesthetization of the trachea and intubation without the cough or bronchospasm incident to light general anesthesia. A further advantage is that respiration may be controlled more easily, the lungs ventilated adequately, and the mediastinum stabilized in the open thorax. The general anesthetic with least effect on the myocardium is nitrous oxide employed with physiologic quantities of oxygen. Although the analgesia provided is good, the agent is not potent, and curare provides the immobilization needed for surgery.

Monitoring of the Vital Signs

A major deficiency in modern anesthetic practice is the lack of simple methods to follow quantitatively changes in the circulation and respiration. Merely determining the blood pressure by auscultation and intermittently taking the pulse rate are not sufficient to follow the course of a patient through operation. Often, hands are not free for these measurements. There are times when the character of the pulse wave precludes determination of the blood pressure by auscultation. Here, the pressure may be taken by palpation, and the patient's wrist must be within reach. Despite this vigilance there should be some independent, continuous monitoring device. We have found the electrocardiogram continuously made visible on an oscilloscope a helpful means to this end. From many illustrative cases 1 life-saving example is presented.

Case 8. E. D. (P.B.B.H. 9G633), a 40-year-old man, had had a known bout of rheumatic fever at the age of 5 and a subsequent limitation of activity throughout his life. At the age of 36 attacks of dizziness and palpitation were followed by a cerebrovascular accident. He became more and more limited by fatigue and then by paroxysmal attacks of dyspnea and ultimately was totally exhausted at the end of the day. On examination the heart was enlarged. Murmurs suggested multivalvular disease, chiefly aortic insufficiency and mitral stenosis. The heart was fibrillating, and the blood pressure was 190/50. The peripheral pulses were of the Corrigan type, with pistol-shot sounds. Fluoroscopy revealed an enlarged left ventricle, with calcification of the aortic and mitral valves. Exercise brought the pulmonary capillary blood pressure to levels of pulmonary edema. Exploratory cardiotomy was planned to determine the degree of mitral stenosis, aortic stenosis and aortic insufficiency. Pressure gradients were to be taken across the aortic valve. A prosthetic aortic valve for aortic insufficiency was ready. After administration of 100 mg. of pentobarbital and 75 mg. of meperidine for preoperative medication he underwent an uneventful induction of anesthesia with cyclopropane followed by ether. As anesthesia was deepened the heart rate was noted to lessen on the

electrocardiogram. The anesthetic was discontinued, and the lungs ventilated with oxygen, but the heart came to a standstill. The surgeon stimulated the heart with a blow to the precordium and direct needle puncture through the intact chest. Cardiac activity immediately returned, and the operation was canceled. After a delay in awakening the patient recovered his preoperative state.

It seems fairly obvious that cardiac arrest was due to overdosage with the anesthetic agent and that a temporary high blood level of the drug depressed the myocardium. The oscilloscope renders arrhythmias, changes in conduction mechanisms and myocardial ischemia immediately apparent. Without the electrocardiogram, drugs for the treatment of arrhythmias cannot be rationally or safely employed. The electroencephalograph is another means of monitoring an anesthetic. This is valuable in the detection of changes in the brain from arterial blood anesthetic levels, varying cerebral oxygenation and cerebral blood flow. Artusio[15] has pointed out that this is the best means of avoiding the transient high blood levels of ether that depress the myocardium. He has also seen warning electroencephalographic signs of cardiac difficulty before changes were apparent in the electrocardiogram.[16] In special situations such as the hypothermic state, in which the blood pressure may be difficult to hear or palpate because of an altered pulse contour, a continuous recording of the brachial-artery pressure through an indwelling cannula can be utilized. In the absence of these several instruments the best the anesthetist can do is to keep his finger on the pulse and observe the heart through the open thorax.

A valuable sign in the detection of cerebral hypoxia is the size of the pupil. Dilatation occurs promptly when the circulation or oxygenation of the brain becomes inadequate. We have observed cases in which the efficacy of manual restoration of cardiac systole during cardiac arrest could be gauged accurately by pupillary dilatation and constriction.

Cardiac Arrhythmias and Arterial Hypotension

Cardiac irritability is the major problem once operation has begun. Actually, irritability and arterial hypotension are interdependent complications. Reference has already been made to some of the factors that may lead to dangerous arrhythmias, hypotension and cardiac arrest. A full discussion of this problem is beyond the scope of this paper. We believe that serious cardiac arrhythmias are rare in the well prepared patient with effective pulmonary ventilation. The following case of Grade 4 mitral stenosis, illustrating the manner in which technical difficulties led to hypoxia and a nearly fatal arrhythmia, is pertinent because the role of hypoxia is so obvious.

Case 9. M. L. (P.B.B.H. 5G290), a 60-year-old woman with the heart murmur of mitral stenosis since childhood, had had progressive fatigue, dyspnea on exertion and attacks of "bronchitis" since the age of 54. Atrial fibrillation and hypertension were found in that year, and digitalis and diuretics were started. At some time later she was treated with propylthiouracil for suspected hyperthyroidism. When seen in the hospital she appeared chronically ill and poorly nourished. The ocular fundi revealed arteriosclerosis. The heart was enlarged. Systolic and diastolic murmurs were heard at the apex. The blood pressure was 200/90. The liver margin was at the umbilicus. Atrial fibrillation and changes consistent with an old anterior septal infarction were seen on the electrocardiogram. The vital capacity was only 680 ml. Mitral valvuloplasty was scheduled. Despite a large quantity of medication, pentobarbital, 100 mg., and morphine, 6 mg., induction of anesthesia was uneventful. But there was difficulty in intubating the trachea, and ventricular tachycardia developed. The operation was canceled. Postoperatively respiratory insufficiency and excessive secretions necessitated a tracheostomy.

Hypoxia and reduced coronary blood flow are the main causes of arrhythmias. This seems quite obvious, but pulmonary ventilation may not conscientiously be performed by the unconcerned anesthetist. Every anesthetist confidently believes that he appreciates these factors and adequately controls them. Unfortunately, there is no way to standardize his efforts. For this reason some prefer to use pulmonary ventilating machines rather than to trust the hand manipulating the anesthetic reservoir bag.

We hope that soon simple devices will be available to give a continuous indication of arterial or alveolar gas tensions. Other things being equal, arrhythmias arising during operation are often of mechanical origin.[17] As the heart is manipulated extrasystoles are produced. Surprisingly enough the heart becomes tolerant of manipulation. If the extrasystoles persist the operator should stop for a moment. Quinidine, procaine and procaine amide will not prevent these myocardial responses. Indeed, the routine use of these myocardial depressants may lead to a situation in which an effective force of cardiac contraction is lacking. Resuscitation of the heart in standstill is more difficult in this circumstance.

When it comes to the choice of a vasopressor agent to treat arterial hypotension it becomes increasingly apparent that a drug with a positive inotropic action on the myocardium may be the choice rather than one acting solely on the peripheral arterioles.[18] Pertinent experimental work can be confirmed clinically by observation of the action of these drugs on the poorly pumping heart in the operative field.

Unfortunately, too little has been added to the treatment of ventricular fibrillation in the severely damaged heart. Although electric defibrillators have become more powerful and theoretically more effective the pharmacologic means of defibrillation are confused and by no means standardized. Ventricular fibrillation in the badly damaged myocardium is truly delirium cordis, which more often than not resists correction.

Summary and Conclusions

Cases selected from a large experience with intracardiac surgery for acquired heart disease are pre-

sented to illustrate some of the problems of anesthetization. The common denominator was that as a group these patients were poorer risks than are generally accepted for surgery. In this type of case any dereliction in anesthetic technic or any harmful characteristic of the anesthetic produced exaggerated responses or fatal issue.

Until an entirely new form of anesthesia replaces the time-worn depression of the central nervous system with potent drugs there will be unsolved problems. The old anesthetics are administered with greater safety now because of better understanding of their pharmacologic action and better means of monitoring their effects in man. The chief problems are those of preparation of the patient for anesthesia, the selection of the least harmful preoperative medication, the choice of anesthetic agent and the technic of anesthesia utilized. In the last analysis it is a knowledge of the patient and his disease that leads to the correct choice. Thus, one cannot speak in terms of an anesthetic agent that is useful and safe in all situations but rather in terms of a method for the particular patient. There are basic rules to be followed in all anesthetics, and the anesthetist must be versatile in his technics.

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SEROTONIN, ANTISEROTONINS AND HYPERTENSION*

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SEROTONIN or 5-hydroxytryptamine (5-HT) (Fig. 1) has been the subject of a great deal of recent investigation and speculation. Two excellent reviews, one by Page[1] and the other by Erspamer,[2] both of whom have contributed important basic information, give the background of the recent interest. Serotonin is found in many tissues of the body but is particularly concentrated in the brain, the platelets of the blood and the mucosa of the gastrointestinal tract. It is an intense local vasoconstrictor, and its presence in platelets has been assumed to give them a styptic as well as a thrombotic function. Certainly within the platelets and perhaps within all its natural locations serotonin must be "bound" or "anchored" in some chemically protected form that defends it from rapid destruction by the amine oxidase of the blood. For this enzyme quickly metabolizes "free" serotonin to 5-hydroxy-indoleacetic acid (Fig. 2), which is promptly excreted in the urine.

Action

What role does serotonin play in its two other principal sites of distribution, the brain and the gastrointestinal tract? In the latter, serotonin and synthetic 5-HT have been shown to be identical chemically with "enteramine," described earlier by Erspamer. This substance was supposed to originate in the enterochromaffin-cell system and was shown to have a strong stimulating effect on smooth muscle of the gastrointestinal tract, and thus possibly to have a regulating effect on gastrointestinal "tone."

The more fascinating question has had to do with the function of serotonin in the brain. Pharmacologic studies were of little aid here because serotonin not

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Supported in part by a grant from the National Heart Institute, National Institutes of Health, United States Public Health Service.

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only is promptly metabolized by the amine oxidase of the blood but also presumably passes the blood-brain barrier with great difficulty if at all. Hence, one cannot expect to determine its effects on central-nervous-system function simply by giving it intravenously. However, one can speculate that it may play a role in central neurotransmission in a manner analogous to that of acetylcholine in peripheral neurotransmission. Thus, it may be liberated momentarily in a free or active form, and then be promptly destroyed.

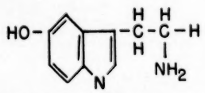

FIGURE 1. *Chemical Structure of Serotonin (5-Hydroxytryptamine).*

Nature has provided at least one fascinating demonstration of the confusing pharmacology of serotonin in the recently described cases of malignant carcinoid of the small intestine, a metastasizing tumor that produces large amounts of serotonin. As mentioned by Thorson and his colleagues[3] in their original description of this lesion associated with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defect), peripheral vasomotor symptoms, bronchoconstriction and an unusual type of cyanosis, this syndrome may result from the pharmacologic effects of serotonin released by the tumor. Waldenström and Ljungberg,[4] Page

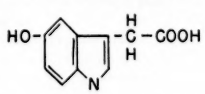

FIGURE 2. *Chemical Structure of 5-Hydroxyindoleacetic Acid.*

et al.,[5] Sjoerdsma, Weissbach and Udenfriend,[6] using chemical methods, have demonstrated a high level of serotonin in the blood as well as in the tumors of these patients, who also excrete a large amount of the serotonin metabolite, 5-hydroxy-indoleacetic acid, in the urine. These workers have also pointed out that the diarrhea, bronchoconstriction and vasomotor disturbances seen in cases of malignant carcinoid are explicable as direct pharmacologic effects of serotonin as judged by its effects when given intravenously in man.

Effects of Serotonin and Antiserotonins on Hypertension

Our interest in serotonin was stimulated by its possible relation to the mechanism of action of Rauwolfia and the pure alkaloid reserpine, which my associates and I introduced into this country for the treatment of hypertension in 1951 and 1952.[7-13] The slowness of the onset of action of the Rauwolfia preparations suggested that they might work through some hormonal or other intermediate mechanism. When the chemical structure of reserpine (Fig. 3) was shown, in 1953,[14,15] to resemble that of yohimbine and, indeed, to contain the nitroindole structure of serotonin, one had a basis for the speculation that reserpine might act through potentiating, or possibly even antagonizing, the effects of serotonin. Dr. D. W. Woolley, of the Rockefeller Institute in New York, in 1954, called attention to his papers[16-19] on various structural analogues of serotonin, including yohimbine, which he showed may act pharmacologically as "antiserotonins," and in 1952 had postulated might be useful chemically as antihypertensive agents.[16] He expressed the opinion that reserpine might be such a structural analogue of serotonin. Dr. Woolley then supplied us with his compound, 2-methyl-3-ethyl-5-nitroindole (Fig. 4), which we tried in 6 of our patients with well known

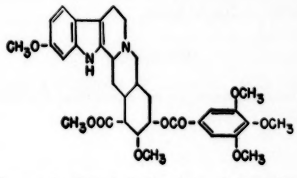

FIGURE 3. *Chemical Structure of Reserpine.*

hypertension. They were able to tolerate the drug in the dosage used for only three to eight days because of its side effects of mental depression, insomnia, nausea, diarrhea and abdominal cramps. The drug had no hypotensive effect on these patients.

Shortly after this experiment in 1954 Dr. J. R. Smythies sent us a copy of a paper[20] in which he had collaborated that called attention to the chemical similarity between adrenochrome (Fig. 5) and other reportedly hallucinogenic substances such as mescaline, harmine, yohimbine and lysergic acid, all of which, like adrenochrome (and serotonin), are known to have an indole nucleus. Dr. Woolley had suggested that serotonin might be involved in mental disorders. Since reserpine is useful in allaying various psychiatric disturbances, it occurred to us that it might act by affecting indole derivatives such as those mentioned by Dr. Smythies or serotonin itself as suggested by Dr. Woolley.

Our speculations on the possible interrelations of reserpine and these various indole derivatives were further stimulated by the recent work of Brodie and his collaborators at the National Heart Institute. These workers, with a newly perfected spectrophoto-

fluorometer,[21] were able to measure the concentration of serotonin present in brain, intestine and platelets and the effects of reserpine upon this concentration, as well as upon the urinary excretion of 5-hydroxy-indoleacetic acid, the major metabolite of serotonin. They showed that reserpine causes a marked decrease of serotonin in brain, intestine and platelets, as well as a marked increase in urinary excretion of 5-hydroxy-indoleacetic acid.

Furthermore, they showed that serotonin in large doses potentiates the depressing effect of hexobarbital and of ethanol in animals, as reserpine does, but that lysergic acid diethylamide antagonizes this potentiating action of both other drugs.[22] These workers have stated that their results suggest to them that some of the effects of reserpine may be mediated through the freeing of serotonin from its bound to its active form, resulting first in serotonin action and then in serotonin depletion from its natural storage sites.

In 1955 Dr. Woolley was able to supply us with a new, orally active benzyl analogue of serotonin (1-benzyl-2,5-dimethylserotonin hydrochloride) (Fig. 6)

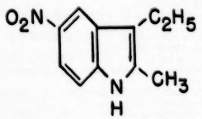

FIGURE 4. *Chemical Structure of 2-Methyl 3-Ethyl 5-Nitroindole.*

referred to as BAS.[23] At almost the same time we were supplied by the Upjohn Company with its serotonin analogue U-4636 (1-ethyl-3-[2-dimethylamino-1-hydroxyethyl]-indole). In animals the first had been shown to be an antiserotonin, and the second to have antihypertensive properties. We gave both of them orally to groups of our patients who were known to have serious hypertension. We have also given BAS and the antiserotonin preparation Ro 2-4394/2 (1-N′ [diphenylacetyl]-1-phenyl-N¹, N², N² trimethyl-1,2-propanediamine phosphate)* to such patients intravenously. The effects of all these chemically similar agents will be reported in detail elsewhere.[24] Suffice it to say here that only the BAS obtained from Dr. Woolley seemed to have possibilities as a practical hypotensive agent when given to hypertensive patients by mouth for periods of two to four weeks (with interruptions by placebo control observation).

We have now had a total of six months' experience with BAS in a total of 25 hypertensive patients. It has been most interesting to observe that BAS given orally has effects remarkably similar to those of reserpine. Thus, as compared with placebos, it causes a definite, though moderate, lowering of blood pressure (average of 20/15 mm. of mercury), without serious side effects (Fig. 7). The side effects, like those of reserpine, include sedation or sleepiness, some slowing of the pulse, mild nasal congestion and increased motility of the bowel occasionally associated with abdominal cramps. Its effective dosage range, unlike that of reserpine, is quite limited, from 40 to 160 mg. a day (in four equally divided doses), beyond which it usually causes intolerable sedation.

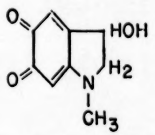

FIGURE 5. *Chemical Structure of Adrenochrome.*

Given intravenously, BAS in our experience also is, as Woolley demonstrated it to be in animals, definitely an "antiserotonin" in that it blocks the pressor reaction as well as the respiratory response to intravenously administered serotonin. Investigations are now under way in this laboratory to determine whether its apparently desirable hypotensive effect after oral administration in hypertensive patients is also associated with demonstrable "antiserotonin" action as judged by blockade of the pressor and respiratory effects of serotonin injected intravenously.

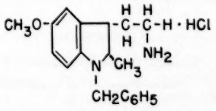

FIGURE 6. *Chemical Structure of the Benzyl Analogue of Serotonin (BAS).*

DISCUSSION

These are matters of considerable theoretical importance because a decision should now be made whether reserpine and other possible analogues of serotonin, including BAS, are hypotensive and sedative because they act as antagonists to serotonin, in accordance with Woolley's views, or because they have pharmacologic properties similar to or possibly even potentiating those of serotonin, as in Brodie's view. In this connection it is interesting that the Sandoz preparation, BOL, which is identical chemically with lysergic acid except for a bromine in the 2 position, and is similar to it pharmacologically in being a strong antiserotonin in vitro, is said when used clinically to act in a manner opposite to lysergic acid in that it produces no mental disturbance, but on the contrary, causes sedation as reserpine does.[25]

*Kindly supplied by Hoffmann-La Roche, Incorporated, Nutley, New Jersey.

It should therefore be remembered that the clinical actions of all these new "antiserotonin" agents in the doses that can be tolerated by patients may have nothing at all to do with specific serotonin effects but may be related to some other associated pharmacologic action. Nevertheless, these are questions of more than theoretical interest because the search for other drugs with either antihypertensive or tranquilizing properties will be greatly expedited if a sound theoretical basis for such actions can be established. Serotonin and antiserotonins seem destined to figure prominently in these questions for some time to come.

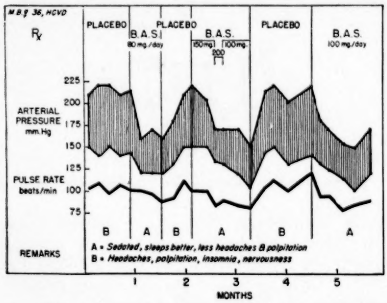

FIGURE 7. *Effect of Oral Doses of BAS on the Blood Pressure and Pulse Rate of a Patient with Hypertensive Cardiovascular Disease.*

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PROPHYLAXIS OF ISONIAZID NEUROPATHY WITH PYRIDOXINE*

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SHORTLY after the introduction of isoniazid in 1952, Pegum[1] described a patient who after a week of therapy with this drug complained of "burning feet"; he suggested that induced nicotinic acid deficiency might be the cause. Later, McConnell and Cheetham[2] reported a case of "acute pellagra" complicating therapy with isoniazid that responded to nicotinic acid and a preparation containing vitamin B complex. In 1953 Jones and Jones[3] presented 2 cases of peripheral neuropathy in isoniazid-treated patients; 1 of these had signs of pellagra that responded to nicotinamide, after failing to improve on thiamine. These authors also suggested that pyridoxine (vitamin B_6), chemically related to both

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nicotinamide and isoniazid, may be the deficient factor — the utilization of which might be antagonized by isoniazid. Biehl and Skavlem,[4] in a preliminary report, and later Biehl and Vilter,[5] in a completed study, showed that peripheral neuropathy occurred in 14 of 36 patients who received 20 mg. per kilogram of body weight per day within four to eight weeks. No cases of peripheral neuropathy occurred in 20 patients who were treated with the same dosage of isoniazid combined with 300 to 400 mg. of pyridoxine per day. The same authors also demonstrated that the administration of isoniazid significantly increased the excretion of vitamin B_6 in the urine. Peripheral neuropathy has also been reported as one manifestation of the pyridoxine-deficiency state that can be experimentally induced in man by a pyridoxine antagonist, desoxypyridoxine.[6] The frequency and severity of peripheral neuropathy during isoniazid treatment is apparently related to the dosage of isoniazid; higher doses are associated with greater frequency and severity of this complication.[5,7]

It has been shown that concentrations of pyridoxine far in excess of those obtained in vivo fail to modify the antimicrobial action of isoniazid on tubercle bacilli in vitro,[8,9] nor does it affect the chemotherapeutic activity of isoniazid in laboratory animals challenged with a standard strain of virulent tubercle bacilli.[9,10] The administration of pyridoxine in doses up to 200 mg. per day does not affect the isoniazid blood levels as determined by microbiologic assay in human beings.[11] Thus, the administration of pyridoxine does not interfere with the chemotherapeutic activity of isoniazid.

It was the purpose of this study to determine the number and character of peripheral neuropathic reactions in a large group of patients receiving isoniazid in dosages of 8 to 16 mg. per kilogram of body weight per day, with concomitant pyridoxine in daily dosages of 25 mg. or more.

Materials and Methods

All adult patients included in this study were admitted to National Jewish Hospital between January 1, 1954, and June 1, 1955, and received doses of isoniazid of 8 mg. or more per kilogram of body weight per day in combination with pyridoxine, 25 mg. or more per day, for at least 2 months.

Since early in 1954 it has been the practice at this hospital to administer pyridoxine to all patients receiving isoniazid. Pyridoxine was routinely administered in one dose of 25 mg. per day for those taking 8 mg. of isoniazid per kilogram of body weight and 50 mg. per day for those taking more than that amount.

Thiamine was routinely included in the treatment of these patients. With the exception of 1 case (Case 7 reported below), the other components of the vitamin B complex were not administered during the period of observation.

All patients who voiced complaints that could conceivably be attributed to neuropathy from the administration of isoniazid are included. Neurologic examinations were performed at the time of the complaint and in most cases were followed closely by repeated examinations. Leading questions were carefully avoided at all times. Every patient who manifested signs or symptoms of isoniazid neuropathy at any time after the initiation of treatment is also included.

Results

Two hundred and seventy-four patients met the requirements for inclusion in this study. They represent a total of 1757 patient months of therapy and observation.

One hundred and seventy-five patients were treated with 8 mg. of isoniazid per kilogram of body weight per day. They represent 1245 patient months. The average duration of treatment for this group was 7.1 months, with a range of 2 to 17 months.

Ninety-six patients were treated with 16 mg. of isoniazid per kilogram of body weight per day, representing 485 patient months. The average duration of therapy of this group was 5.1 months, with a range of 2 to 10 months. Three additional patients received 12 mg. for an average of 9 months, with a range of 5 to 12 months.

One of the 274 patients discussed here received para-aminosalicylic acid during his period of observation. Para-aminosalicylic acid is known to affect the metabolism of isoniazid.[12] Nearly all the patients received streptomycin for various periods and at various dosages.

There were 8 patients in the group receiving 16 mg. and 3 in the group receiving 8 mg. per kilogram of body weight per day who complained of symptoms suggestive of isoniazid toxicity. These 11 cases are reported here in detail.

Case Reports

Case 1 (N.J.H. 11921). A 44-year-old Negro was admitted to the hospital on August 18, 1954, with far-advanced, active, pulmonary tuberculosis. He was treated with 16 mg. of isoniazid per kilogram of body weight per day, in combination with 25 mg. of pyridoxine daily beginning on August 24. Six months later he complained of paresthesias of the soles of both feet. Isoniazid was suspended for several days, and 100 mg. of pyridoxine was given intramuscularly each day. The symptoms subsided, and he was again treated with isoniazid in the same dosage, in combination with 100 mg. of pyridoxine. There was no recurrence of symptoms, and he did not manifest a neurologic deficit in spite of subsequent prolonged administration of 16 mg. of isoniazid per kilogram of body weight per day with 100 mg. of pyridoxine per day.

It seems likely that this represented a bona fide case of isoniazid toxicity attributable to an inadvertently low dosage of pyridoxine.

Case 2 (N.J.H. 11962). A 34-year-old Negress was admitted to the hospital on October 11, 1954, with far-

advanced, active, pulmonary tuberculosis. On admission 8 mg. of isoniazid per kilogram of body weight per day was started in combination with 25 mg. of pyridoxine daily. On April 24, 1955, the dose of isoniazid was increased to 16 mg. per kilogram of body weight per day, and that of pyridoxine to 50 mg. daily. Four months later she complained of numbness of the hands and feet, with typical glove-and-stocking distribution. Microbiologic assay of the blood levels of isoniazid showed that this patient metabolically inactivated isoniazid at such a slow rate that a dose of 8 mg. per kilogram of body weight per day was deemed therapeutically adequate. Therefore, the daily dosage of isoniazid was reduced to this amount and that of pyridoxine increased to 100 mg. The symptoms subsided and did not recur; no neurologic defect was demonstrated at any time.

It seems fair to consider this case a bona fide example of early peripheral neuropathy in a patient who required a dosage of pyridoxine higher than the routine dosage administered at this hospital.

CASE 3 (N.J.H. 11896). A 25-year-old woman was admitted to the hospital on July 19, 1954, with far-advanced, active, pulmonary tuberculosis. On August 3, 8 mg. of isoniazid per kilogram of body weight per day, combined with 25 mg. of pyridoxine daily, was begun. On April 30, 1955, the isoniazid was increased to 16 mg. per kilogram of body weight, and the pyridoxine to 50 mg. daily. Two months later she complained of "numbness all over her body." The isoniazid was discontinued, with subsequent relief of symptoms. Several attempts to administer isoniazid again resulted in the same complaints. At present, although isoniazid therapy has been continued, the patient interrupts her own therapy when symptoms recur. No neurologic deficits were demonstrated.

This patient was a highly emotional, highly suggestible young woman with many personal problems whose symptomatology was extremely difficult to evaluate. It is significant, furthermore, that her complaints did not correspond to the ordinary peripheral pattern of isoniazid polyneuropathy.

CASE 4 (N.J.H. 11993). A 45-year-old man was admitted to the hospital on November 22, 1954, with far-advanced, active, pulmonary tuberculosis. Twelve days later 16 mg. of isoniazid per kilogram of body weight per day and 25 mg. of pyridoxine daily were started. The pyridoxine was increased to 100 mg. daily 2½ months later after the patient complained that his feet felt as if he were "walking on stumps." The pyridoxine was later increased to 200 mg. daily. He still complained of some feeling of numbness in his feet. Subsequently, the severity of these symptoms decreased remarkably. No neurologic deficit was demonstrated, and the isoniazid dosage was not changed.

The initial dosage of pyridoxine was inadvertently less than that routinely employed. It is significant that with no change in therapy, except for an increase in the dosage of pyridoxine, the symptoms abated, although slowly.

CASE 5 (N.J.H. 12088). A 30-year-old woman was admitted to the hospital in March, 1955, with far-advanced, active, pulmonary tuberculosis and diabetes mellitus. She had had severe, "brittle" diabetes since the age of 12. She was treated immediately with 16 mg. of isoniazid per kilogram of body weight per day in combination with 50 mg. of pyridoxine daily. On May 20 she complained of numbness and tingling of the hands and feet. The dose of isoniazid was reduced to 8 mg. per kilogram of body weight per day, and that of pyridoxine was increased to 200 mg. daily. Several attempts to increase the dosage of isoniazid resulted in a return of symptoms. She had several fleeting episodes of tingling in her hands. No neurologic deficit was demonstrated.

In this case, intermittent episodes of symptoms suggestive of peripheral neuritis occurred on 8 mg. of isoniazid per kilogram of body weight per day, without progression or objectively demonstrable neuropathy. It may be significant that this patient metabolized isoniazid to microbiologically inactive derivatives at an extremely rapid rate.

CASE 6 (N.J.H. 10353). A 48-year-old man was admitted to the hospital on February 3, 1955, with far-advanced, active, pulmonary tuberculosis. He had had severe diabetes for many years and on admission demonstrated proteinuria, hypertension and the residue of a left-sided cerebrovascular accident. Treatment with 16 mg. of isoniazid per kilogram of body weight per day, combined with 100 mg. of pyridoxine daily, was started on March 4. Three months later, he complained of a pins-and-needles sensation in the hands, burning of the dorsum of both feet and numbness of the soles of both feet. The dosage of pyridoxine was increased to 200 mg. daily and the isoniazid was suspended for 6 days, with disappearance of symptoms. On September 3 the symptoms recurred, and the patient of his own accord did not take the isoniazid for 6 days until the symptoms once more subsided. At no time did he manifest any motor or sensory loss on neurologic examination.

Peripheral neuritis, common in diabetes, has been shown to occur frequently in diabetic patients treated with isoniazid.[9] The fact that this patient never demonstrated positive neurologic findings in spite of continuation of therapy is worthy of emphasis.

CASE 7 (N.J.H. 12169). A 30-year-old Negro was admitted to the hospital on May 28, 1955, with far-advanced, active, pulmonary tuberculosis. This patient presented a definite alcoholic background and was moribund, with marked cachexia, subnormal temperature, bradycardia and a hemoglobin of 7.9 gm. per 100 ml. On admission he was treated with 12 mg. of isoniazid per kilogram of body weight per day combined with 100 mg. daily of pyridoxine and massive doses of other vitamins. Within a few weeks he complained of numbness of the feet that has persisted to date without progression and without any demonstrable neurologic abnormality. Treatment has been continued without change in the dosage of isoniazid or pyridoxine.

It is known that peripheral polyneuropathy occurs commonly in alcoholism and is usually made more severe by isoniazid.[9] In this case the complaints were probably attributable to an alcoholic neuritis established before the administration of isoniazid. It seems important that with pyridoxine the neuropathy did not progress in spite of administration of isoniazid in a dosage of 12 mg. per kilogram of body weight per day.

CASE 8 (N.J.H. 12123). A 26-year-old Spanish-American woman was admitted to the hospital in April, 1955, with moderately advanced pulmonary tuberculosis. On May 31, 1955, 16 mg. of isoniazid per kilogram of body weight per day with 50 mg. of pyridoxine daily was started. Eleven days later she complained of numbness of the hands, feet and tip of the tongue. Isoniazid was discontinued, with relief of symptoms. Therapy was restarted on June 21 in a dose of 4 mg. of isoniazid per kilogram of body weight per day and 200 mg. of pyridoxine daily, and symptoms recurred on July 18, accompanied by a moderately severe anxiety reaction forcing interruption of therapy. Another attempt to resume isoniazid resulted in a similar reaction.

Even the suggestion that isoniazid be continued was followed by a severe anxiety reaction on the part of this patient and made further therapy with this

drug impossible. It seems likely that the original symptoms were a manifestation of peripheral neuropathy due to isoniazid. Furthermore, the anxiety might be attributable to this drug: anxiety states have been elicited in some human beings by isoniazid.[13,14]

CASE 9 (N.J.H. 12045). A 48-year-old woman was admitted to the hospital on January 2, 1955, with tuberculosis of the dorsal spine and right hip. She was treated with 16 mg. of isoniazid per kilogram of body weight per day combined with 50 mg. of pyridoxine daily. She was a very obese woman, weighing over 113.4 kg. (250 pounds); the total daily dose of isoniazid was 1800 mg. The total daily dose of streptomycin was 2 gm. Within 2 weeks, she complained of being extremely sleepy and had a pins-and-needles sensation in the hands and hips, followed by numbness in the same areas. Her tongue felt as if it were "too big for her mouth." The isoniazid was reduced to 8 mg. per kilogram of body weight per day, and the pyridoxine was increased to 100 mg. daily. The streptomycin was also reduced to 1.0 gm. daily. There was no recurrence of symptoms. No neurologic deficit was demonstrated.

This patient was on excessively high dosage not only of isoniazid but also of streptomycin as well. Since both drugs were reduced in dosage as a result of this somewhat atypical symptom complex, it is not possible properly to assess the role of isoniazid. She subsequently tolerated 900 mg. of isoniazid combined with 100 mg. of pyridoxine daily, without further symptoms referable to isoniazid toxicity.

CASE 10 (N.J.H. 11789). A 26-year-old Negro was admitted to the hospital on March 18, 1954, with far-advanced, active, pulmonary tuberculosis. He gave a history of having been a heavy drinker for at least 5 years. Shortly after admission he was treated with 8 mg. of isoniazid per kilogram of body weight per day, without pyridoxine. On September 3, pyridoxine, 25 mg. daily, was added to the regimen. On May 25, 1955, he underwent resection of the right upper lobe, followed by a space-reducing thoracoplasty. On August 3 he complained of numbness along the extreme ulnar surface of the right hand, without objective findings. The isoniazid was reduced to 4 mg. per kilogram of body weight and the pyridoxine was increased to 50 mg. daily. He continued to have numbness in the same region, without demonstrable sensory loss.

In view of the operative procedure in the region of the brachial plexus, it would be extremely difficult to consider the drug responsible for this patient's ulnar mononeuropathy.

CASE 11 (N.J.H. 12094). A 50-year-old woman was admitted to the hospital on March 4, 1955, with far-advanced, active, pulmonary tuberculosis. On admission she was treated with 16 mg. of isoniazid per kilogram of body weight per day in combination with 100 mg. of pyridoxine daily. Two months later she complained of numbness and tingling "all over her body" and, 1 week later, of failing vision. She was examined by an ophthalmologist, who noted "some hyperemia of the disk on the right." She was seen later by the same ophthalmologist, who observed "temporal pallor on the right and hyperemia of the disk on the left — neither of which was present on the original examination." He considered the findings compatible with optic neuritis. Isoniazid therapy was discontinued at once. The visual acuity is now correctible to 20/25 on the right and 20/20 on the left. No further attempt was made to administer isoniazid to this patient.

Optic neuritis has been described in isoniazid-treated patients. Two case reports have appeared.[15,16] In both, the patients were receiving only 200 mg. per day. It seems reasonable to consider this complication an absolute contraindication to continuation of the drug if the presence of optic neuritis can be confirmed in any patient receiving isoniazid.

DISCUSSION

In many tuberculous patients, isoniazid is so rapidly metabolized to antimicrobially inactive derivatives that doses of 3 to 5 mg. per kilogram of body weight per day are therapeutically inadequate.[17,18] Peripheral polyneuropathy has been by far the most frequent significant toxic reaction occurring during therapy with isoniazid. Previous experience has established the occurrence of peripheral polyneuropathy in patients treated with isoniazid in daily doses of 8 mg. or more per kilogram of body weight.[4,5,9] In many cases, the neuropathy thus produced has been severe enough to require that the drug be discontinued. Thus, many patients, because of a disabling peripheral neuropathy, might be denied effective doses of the most potent chemotherapeutic agent available for tuberculosis.

The prophylactic effect of pyridoxine in prevention of peripheral polyneuropathy was the subject of this study. Of primary importance, we believe, is the absence of significant neuropathy in patients receiving adequate dosage of pyridoxine along with 8 to 16 mg. of isoniazid per kilogram of body weight per day. In only 2 cases did side effects preclude further administration of isoniazid. In the first a severe anxiety reaction created a relative contraindication. In the other, symptoms and signs of optic neuritis, considered to be a serious, although rare, complication of isoniazid administration, developed.

The complaints of 3 or 4 (Cases 3, 8 and 11, and possibly 6) of the 11 patients described above were consistent with the psychologic effects of isoniazid reported by other investigators.[13,14] It has been suggested[3,14] that nicotinamide (or nicotinic acid) may alleviate these psychologic disturbances. This vitamin was not employed in the cases reported above.

Eight patients who complained of symptoms compatible with peripheral neuritis continued to tolerate isoniazid by virtue of increased dosage of pyridoxine after symptoms had first appeared. In these patients progression in symptomatology did not occur — nor were neurologic deficits objectively demonstrable.

It seems probable that several of the cases presented were not valid examples of peripheral polyneuropathy. In some cases, however, improvement followed the administration of larger doses of pyridoxine, of smaller doses of isoniazid or both, suggesting that the symptoms actually were attributable to isoniazid toxicity.

The results of this study indicate that a daily dose of pyridoxine of about 300 mg.[5] is in excess of the amount required by the great majority of patients on 16 mg. of isoniazid per kilogram of body weight per

day. Because of the present high cost of this vitamin, this conclusion has more than academic interest.

Summary

Two hundred and seventy-four patients were treated for at least 2 months (1757 patient months) with 8 mg. or more of isoniazid per kilogram of body weight per day in combination with pyridoxine, 25 to 200 mg. per day. Only eleven (4 per cent) of these patients complained of symptoms suggesting neuropathy attributable to isoniazid toxicity. Eight continued to receive isoniazid without subsequent progression of symptoms or the development of demonstrable neurologic changes.

Peripheral polyneuropathy occurring as a complication of isoniazid therapy did not contraindicate further administration of isoniazid, provided that pyridoxine was included as part of the daily regimen and that the patient was carefully followed.

In the great majority of these adult patients 25 mg. of pyridoxine prevented the appearance of significant peripheral neuropathy when isoniazid dosage was 8 mg. per kilogram of body weight per day, and 50 mg. was adequate for patients being treated with 16 mg. of isoniazid per kilogram of body weight per day.

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SPECIAL ARTICLE

BOSTON MEDICAL LIBRARY

Report of the Librarian*

HENRY R. VIETS, M.D.†

BOSTON

THE Librarian herewith presents his annual report, the eighteenth accounting of the state of the Library since he took office in 1938. The report covers the calendar year 1955, another year of increased attendance following a pattern of an upward trend of usefulness, continuous since the end of World War II. Both the figures for circulation and those for attendance were the largest ever recorded, over 74,000 items being used by more than 17,000 readers. The Library grew in size at its regular rate, adding over 4000 books to reach a total of 228,770 catalogued volumes. With the catalogued pamphlets the Library now has 387,525 items available to its users. Nearly 1 out of 5 items in the entire collection was called for in 1955.

As in the past many books and journals came to the Library as gifts, and we were particularly indebted to the *Journal of Bone and Joint Surgery*, the *New England Journal of Medicine*, the Lahey Clinic, the Mallory Institute of the Boston City Hospital, the Massachusetts Department of Public Health, the University of Maine Library, the Hahnemann Hospital in Worcester, the American Optical Company, the Medical Library of Tufts University, the Armed Forces Medical Library, the Ciba Foundation, the University of California School of Medicine and the Lane Medical Library and to individual donors who

*Presented at the annual meeting of the Boston Medical Library, March 6, 1956.

†Curator, Boston Medical Library.

enriched our collection. We received books and pamphlets from the estates of Timothy Leary and Solomon R. Kagan and numerous items from others, particularly Allan L. Davis, Charles G. Mixter, Arthur B. Lyons, Charles I. Johnson and other friends of the Library.

In addition, accessions were purchased with special funds designated for specific purposes. Some of the principal items are briefly noted below, along with some discussion of their relative importance.

Accessions

Incunabula

Four books printed before 1501 were added: Aristotle, *De regimine principum ad Alexandrum editus* (Leipzig, c. 1490-95); Mesuë, Johannes, *Opera medicinalia* (Pavia, 1478); Antoninus Florentinus, *Summa theologica* (Strasbourg, 1496); and Eyb, Albertus de, *Margarita poetica* (Basel, 1495).

The Mesuë *Opera* is a superb copy, with illuminated initials in dull blue and red, bound in full niger morocco by Sandorski and Sutcliffe in London. The Library also has a later edition of 1497 (Ballard, *Catalogue*, 472). This is the work of Mesuë, junior, a shadowy figure in history, whose writings on Arabic pharmacy and materia medica were frequently printed in the fifteenth century, both in Latin and in Italian. He is not to be confused with Mesuë, senior, the Christian head of the Arabic school at Bagdad and physician to the caliph, Harun-al-Rashid.

The *Summa* of Antoninus contains all five parts in three volumes, the Library having previously the third part only. Complete copies of this edition are not recorded elsewhere in American libraries.

To the collection of manuscripts and incunabula 5 manuscripts and 79 books published before 1500 have been added since Mr. Ballard's *Catalogue* was published in 1944. He listed 52 manuscripts and 674 incunabula. The total has now reached 810, and a list of the added items to form Volume 2 of the *Catalogue* is contemplated. These additions have largely been purchased by funds left by the late Dr. Bullard, but some have been added through the Hyams Fund and a few through general funds left to the Library for this purpose.

English Imprints

A book long desired by the Library was added to the historical collection, over four hundred years after it was first printed in 1552. This is the first medical treatise written and published in English, although a somewhat more extended discussion of the same subject was published by the author in Latin a few years later. The writer, John Caius (Fig. 1), the second founder of Gonville and Caius College at Cambridge University and master of the college from 1559 to 1573, was born in Norwich in 1510, and graduated from Gonville Hall in 1535. He then went to Italy for a long tour, studying medicine at Padua at the time Vesalius was professor of anatomy; indeed, there is some evidence that Caius lived in the same house with Vesalius for eight months. Unfortunately, in spite of this intimacy, Caius does not seem to have fully accepted the new ideas in anatomy promulgated by his Belgian colleague. He lectured in Greek on the logic and philosophy of Aristotle for

Figure 1. *John Keys (Caius) about the Time of the "Sweatyng Sicknesse" — from:* The Works of John Caius, M.D. *(Cambridge, 1912).*

a year or so at Padua before he returned to England. On his way back to London he explored Italy, making observations on the manuscripts that he found in various town libraries. He must have already made a name for himself as a scholar, for at Florence he was the guest of Cosmo de' Medici. He then toured through France and Germany and became acquainted with many of the leading scholars of the day, including Conrad Gesner, who became a lifelong friend. His mind at this time seems to have been taken up mainly with his interest in the Greek language, particularly in its pronunciation, which led to a book on that subject published later in life.

In England he settled in London, where he soon became admitted as a fellow of the College of Physicians, being elected in 1550. He subsequently became president of the College and, indeed, in 1571 was elected for the ninth time to this high office. Caius, a bachelor, lived a solitary and eccentric life in a house in the parish of Saint Bartholomew the Less, and gave large sums of his fortune, which apparently he made in practice and by shrewd investments in real estate, to his college in Cambridge. Most of his benefactions were in the form of manors, originally monastic property, which he bought from Queen

Mary Tudor, whose physician he had become. Even after he became master of Gonville and Caius College he continued to practice in London until he died in 1573.

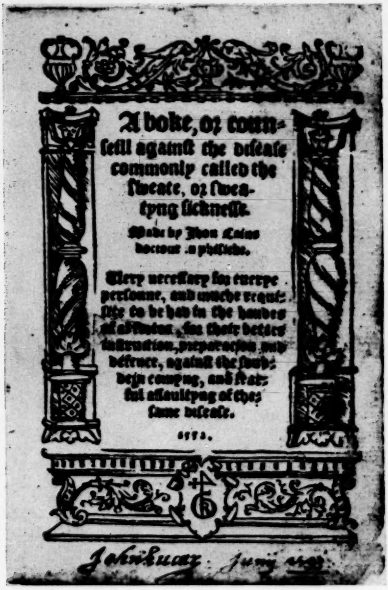
A boke, or counseill against the disease commonly called the sweate, or sweatyng sickenesse.
Made by Iohan Caius doctour in physicke.

FIGURE 2. *Title Page of John Keys's (Caius) — A boke, or counseill . . .* sweatyng sicknesse *(London, 1552).*

The story of his life in Elizabethan England is full of interest and presents many highlights on the activities of a sixteenth-century doctor. Although he had a large practice and apparently was most successful in it, he spent part of his time in philanthropic work. He is best known for his description of the sweating sickness, probably a form of influenza, and his slight treatise, *A boke, or counseill against the disease commonly called the sweate, or sweatyng sickenesse,* was published in April, 1552, by his friend in London, Richard Grafton (Fig. 2). In 1551 the sweating sickness broke out in Shrewsbury. Caius is thought to have actually observed cases of the disease during this epidemic, and perhaps was even in practice in Shrewsbury itself, but the history of his medical activities at that time is not quite clear. In the preface to his book he states:

> I spared not to go to all those that sente for me, bothe poore, and riche, day and night. And that not only to do them that ease that I could, and to instructe them for their recouery: but to note also throughly, the cases and circumstaunces of the disease in diuerse persons, and to understande the nature and causes of the same fully, for so much as might be.

He did not need to go to Shrewsbury to observe cases, for the disease was at its height in London in the middle of July, 1551, and during that month over 800 persons died, 600 within a week.

When the epidemic in London died down in August it is pleasant to think of the alert practitioner as going to the Library of the College of Physicians and looking up all the literature that he could find on this subject. This he reviewed in his book and no doubt took his notes in Latin or Greek from the originals, since he was proficient in both languages. When he came to write up the treatise, having noted that many practitioners were not scholars in the classical languages, perhaps as a result of his lectures to the barber-surgeons on anatomy, he "finished one boke in Englishe, onely for Englishe men not learned, one other in latine for men of lerninge more at large, and generally for the help of them which hereafter should haue nede, either in this or other countreis, that they may learne by our harmes." He expected to have his account ready by Christmas, but like so many authors before and after his time, he was delayed and could not get it ready for the press until April, 1552. Perhaps he had to go back and verify his references in the Library at the College of Physicians. The little book in English is written for the public and thus has a unique place perhaps in English literature as a book designed, without case histories, for the average person to read. The accent is on a description of the disease and particularly on prevention, and he advocates a restriction on the excesses of the time regarding treatment, temperance regarding diet, and the overcoming of fear, which he considers an important cause of some of the symptoms. The book in Latin for the doctors was not finished until January, 1555, and was published the next year in his collected works. For a printer and publisher of the English edition he could hardly have chosen any better than Richard Grafton, the King's printer, whose great Bible of 1539 was purchased by every parish in England, and who published the *Acts of Parliament in 1552,* the year of Caius's book.

Caius rented his house in London in the year 1551, the year in which the epidemic had started in Shrewsbury and spread to London during July. It was one of some twenty houses in the close of Saint Bartholomew that the college was in the habit of letting, the occupants being generally persons of some distinction. So far as is known, however, Caius had no connection with St. Bartholomew's Hospital itself. The house, which does not seem to have been large, must have had a hall of considerable size, for it was spacious enough to accomodate the whole College of Physicians at the first college feast in 1556. Caius returned to this house all during his life, even when he was master of the College at Cambridge, and he died there in 1573. It was from this house, moreover, that he used to go to give his lectures on anatomy to the barber-surgeons, who had a license to claim the bodies

of four criminals a year for dissection. He became physician to three sovereigns in succession, Edward VI, Mary Tudor and Elizabeth I. Just when the house was rented or when he established himself in London in the year 1551 is not clear. It may have been before the April outbreak of sweating sickness in Shrewsbury. He almost certainly went to Shrewsbury, but I judge, from his account in the Latin version, largely as a spectator or perhaps as a consultant.* It is quite possible that most of the cases on which he based his symptomatology were seen in London.

To place Caius in the history of medicine is not a very difficult task. The date, 1552, gives a focal point, and his book, written in English for the reading public and containing observations, however slight, on the disease as it appeared the year before in Shrewsbury and in London, wherever he observed most of his cases, is a landmark in the history of English medicine. It can only be compared with the work of Harvey in 1628 as far as exact dates are concerned, but, of course, the influence of Harvey, also a graduate from Padua, was far beyond anything experienced by John Caius. He was perhaps a little unfortunate, from the point of view of preventive medicine, in that he described a regimen to prevent a disease that never appeared again in a form recognizable as "sweating sickness." On the other hand, he set a style of writing that has been followed ever since by recognized medical authorities writing for the public. At the same time he did not forget his fellow physicians, both in England and abroad, for he wrote his treatise in scholarly Latin, which could be read everywhere by his more learned colleagues. To him this popular little book may well have been incidental, for he was apparently much more interested in the teaching of anatomy, which he must have done in the Galenic tradition without accepting or perhaps even realizing the importance of the work of Vesalius. He thus seems to have missed the most glorious episode that might have occurred during his whole lifetime if he had brought Vesalius and his ideas into active acceptance in London and in England in general. He may, however, have been influential in spreading the subject of anatomy, for no such lectures with human dissections had been given previously in England. They were attended by physicians in considerable numbers over a period of twenty years.

Paris in 1698. One of the most popular of the early travel books by physicians is that of Martin Lister, *A journey to Paris in the year 1698,* published in London in 1699, which became so read that it was issued in three editions within the year (Fig. 3). It is a detailed narrative of all that this London physician of sixty saw in Paris, including an account of many of the museums, the libraries and the gardens, both public and private. Martin Lister was primarily a zoologist and not a physician. Born about 1638 of a Yorkshire family, several members of which became eminent in medicine, he attended St. John's College in Cambridge, where he was graduated in 1659. He was made a fellow of his college and took an M.A.

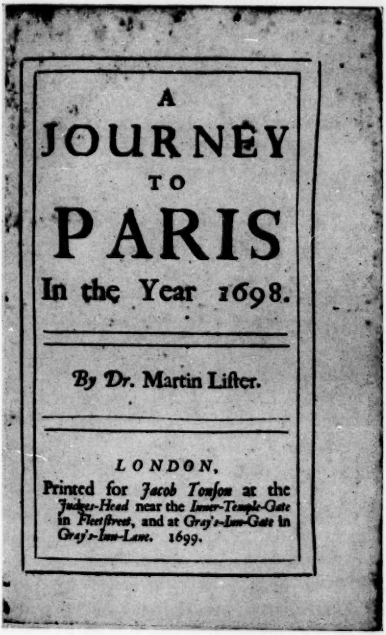
A
JOURNEY
TO
PARIS
In the Year 1698.
By Dr. Martin Lister.
LONDON,
Printed for Jacob Tonson at the Judges-Head near the Inner-Temple-Gate in Fleetstreet, and at Gray's-Inn-Gate in Gray's-Inn-Lane. 1699.

FIGURE 3. *Title Page of Lister's* A journey . . . *(London, 1699).*

degree in 1662. He then traveled abroad, largely devoting himself to natural history, but it is not known whether or not he obtained a medical degree at some European university at this time. At all events he was made a fellow of the Royal Society in 1671 and settled in York, where he practiced medicine with considerable repute for many years. He moved to London in 1684 and was created M.D. by the University of Oxford that year. He then became a fellow of the Royal College of Physicians.

It was in 1698 that he accompanied the Earl of Portland on his embassy to Paris, where he remained six months. As a result of this trip the book on Paris was written. He gives many trivial details, but the minuteness of his descriptions give the book a good deal of historical value. Lister is also remembered for a type of orchid that bears his name, his development of geologic maps, his frequent papers read before the Royal Society and published in the *Philo-*

*Dr. F. N. L. Poynter, librarian of the Wellcome Historical Medical Library, makes a pertinent suggestion in a letter: since the book is dedicated to the Earl of Pembroke, whose house was in Shrewsbury, Caius may have been called to attend the Earl's household during the epidemic. If so, this speaks well for Caius's reputation in 1551.

sophical Transactions, and his books on shells, insects, particularly spiders, and other discourses on natural philosophy.

His travel book was translated into French and published in 1873 by La Société des Bibliophiles. It was edited by four members of the society, and the Library has a most interesting copy belonging to one

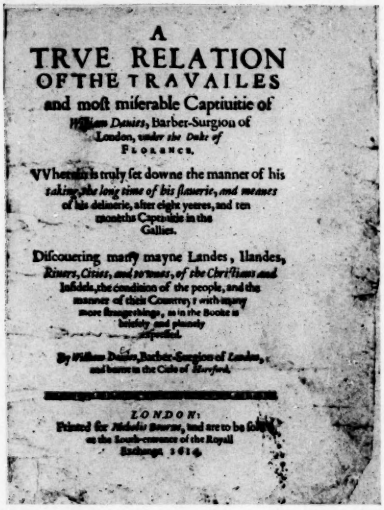
A
TRVE RELATION
OFTHE TRAVAILES
and moſt miſerable Captiuitie of
William Danies, Barber-Surgion of
London, *vnder the Duke of*
FLORENCE.
VVherein is truly ſet downe the manner of his
taking, the long time of his ſlauerie, and meanes
of his deliuerie, after eight yeares, and ten
monthes Captiuitie in the
Gallies.
Diſcouering many ſtrange Landes, Ilandes,
Riuers, Citties, and Fortreſſes, of the Chriſtians and
Infidels, the condition of the people, and the
manner of their Country, with many
more ſtrange things, as in the Booke is
briefly and plainely
expreſſed.
By William Danies, Barber-Surgion of London,
and borne in the Citie of Hereford.
LONDON:
Printed for *Nicholas Bourne,* and are to be ſold
on the South-entrance of the Royall
Exchange. 1614.

FIGURE 4. *Title Page of Dauies's* A trve relation of the travailes . . . *(London, 1614).*

of them, M. le Comte Clément de Ris, beautifully bound in the French style by Dupré and received by le Comte on September 7, 1878, as noted by him on the flyleaf. He has inserted in the volume letters from his three other colleagues, M. Ernest de Sermizelles, le Baron Jérôme Pichon and M. Paulin Paris, regarding the translations. Le Baron Pichon was president of the society the year the book was published. The backstrip of this finely bound book carries the crest of the Comte de Ris with his crown and entwined initials. In addition to the description, for the first time in French, of the voyage of Lister to Paris, there are extracts from the work of the diarist Evelyn concerning his trips to France in 1648 and 1661. Judging by the letters, it is these extracts that gave the editors most of their troubles regarding decisions of how much or how little to include. In addition to the French edition, the Library has all three editions of the book in English published in 1699, as well as the reprint edited by Dr. George Henning in 1823, including a life of Lister.

Another description of seventeenth-century Paris by a young physician of twenty-two was recorded by Edward Browne, son of Sir Thomas Browne, who visited the city in 1664. His account was edited from a manuscript by Geoffrey Keynes and published in the *Saint Bartholomew's Hospital Reports* for 1923.

The Travailes of William Davies. Another early English imprint of considerable rarity and interest is a book entitled *A Trve Relation of the Travailes and Most Miserable Captiuitie of William Dauies, Barber-Surgion of London, under the Duke of Florence,* published in London in 1614 (Fig. 4). In 1597 the barber surgeon from Hereford, William Davies, shipped from Saltash in Cornwall to Italy and Mediterranean ports. He and the crew were captured by the galleys of the Duke of Florence and taken to Leghorn, the port of the city controlled by the duke. He was held there in slavery for more than eight years, the first three at hard labor, and the rest as a galley slave on some of the duke's ships. Finally an English captain employed by the duke suggested that Davies, with his medical training, might be better employed as a surgeon in spite of the fact that he was a Protestant, known as a "Lutheran dogge." He had to put up security of 500 crowns for his liberty, which he obtained from an English merchant. His chains were then struck off, and his red cap and coat denoting his slavery replaced by good clothes. The duke gave him 100 crowns, which he spent on the 13 remaining members of his crew who had survived but who were still slaves — all that were left of the 37 captured eight years before. He succeeded in getting 2 more of them off but had to leave the rest in chains. The ship was well fitted out, and apparently Davies had all the supplies that he needed as a ship's doctor. They sailed to the Amazon on a fruitless voyage of fourteen months, for they found little to gain in South America, and some of them were killed by pirates on the way back to Leghorn. He attended his crew carefully, having been a galley slave himself, and when one of the Englishmen, a Protestant, died he tried to have him buried in a cemetery. This aroused the ire of the Roman Catholic church, and he was thrown into prison, where he remained for a number of months expecting to die, but finally was released with the aid of a passing English master of a ship who had known Davies's brother, who was also a master of a ship out of Plymouth, England.

He had no further adventures so far as captivity was concerned, but he traveled widely and a good part of the book is given up to his descriptions of such places as Algiers, Tunis, Naples, Malta, Cyprus and Sicily. Of greatest interest is his description of the mouth of the river Amazon and the people he found there. Davies was a strong Lutheran who did his best to understand the peoples of the Catholic countries and those who lived under the Turks, the Moors, the Spaniards and the Indians of South America. The book gives a good description of many

lands, for he was an acute observer, particularly of shipping in the Mediterranean, the impressment of seamen, the capture by pirates and the atrocious conditions under which he lived during his captivity. Unfortunately, he does not give details of medical interest, and the account is more a travel book than actually a medical diary. Apparently, he came from a sea-faring family, for he mentioned other members, and it seems certain that the barber surgeon of the early seventeenth century in England was an important part of the ship's crew. Since books of this type must have been popular reading for the English at home not many copies have survived. Fortunately, the Library copy is in excellent condition.

Gesner's Treasures of Evonymvs. The Library also acquired a complete copy of a little book in English by Conrad Gesner, *A new booke of distillation of waters, called the treasure of evonymvs* (London: John Day, 1565). The book, published originally in Latin, was translated by Peter Morwyng, a fellow of Magdalen College, Oxford. This is the second edition in English. Euonymus is a dried preparation from the bark of a tree widely used as a cathartic. It is known as wahoo bark from the name given to it by the American Indians. Gesner's book has largely to do with the distillation of this drug and has numerous woodcuts of the drug and the distillation vessel. The Library also has an incomplete copy of the book, with four pages missed in printing and lacking the index. Because the name of the printer and the date of publication appear at the end of the index there was some doubt about the exact edition. With the newly acquired copy the book can be easily identified as an imperfect copy of the 1565 edition.

Rabelais in Rome. Another book of some interest is *Les lettres de François Rabelais escrites pendant son voyage d'Italie* . . . (Brussels, 1710). It will be recalled that Rabelais (Fig. 5), at the age of about thirty-four, entered the Benedictine monastery of Maillezais near La Rochelle and about 60 miles from Chinon, where he was born. The presiding bishop of Maillezais was a scholar of distinction and became a great friend of Rabelais. After leaving the monastery Rabelais went to Montpellier, where he obtained his doctor's degree in 1530, and thereafter divided his time between the practice of medicine and the profession of editing and publishing books. He was later on the Faculty of Medicine at Montpellier, and many autographs and documents in facsimile regarding his year there were published by the University in 1876.* There, he lectured on Galen and Hippocrates. He was appointed physician to the hospital in Lyons in 1532. It was a natural step for him to edit the works of Hippocrates and Galen when he reached Lyons for the book publishers there. This led to the issuing of a chapbook recalling a story of a giant named Gargantua and later to the expansion of this work and the publication of the famous book about Gargantua's son, Pantagruel, published between 1532 and 1534. These books, in addition to satirizing contemporary religion, politics and social institutions in a characteristic Renaissance variety and

Ille ego Gallorum Gallus Democritus, ille
Gratius aut si quid Gallia progenuit
Ne homines sic et cælestia Numina læsi
Vix homines vix ut Numina læsa premit

FIGURE 5. *François Rabelais — from* Les lettres de François Rabelais . . . *(Brussels, 1710).*

richness, were important in developing the French language, to which they added more than 600 words. The books, however, were condemned by the Sorbonne and prohibited for sale. It is possible that Rabelais had to go to Rome to make his peace with the Church. At all events, he was there with his friend, Du Bellay, who later became a cardinal, and the letters published in the book acquired by the Library are an account of his Roman experiences written to his old friend, the Lord Bishop of Maillezais. For a time he could not practice medicine, but apparently the ban was lifted, for he became city physician of Metz in 1550. To clear himself Rabelais elected to have the accusations tried in court and not privately before the Pope. This was because if a verdict was favorable he could not be retried, whereas a private transaction "in chamber" could always be called into question and tried over again. The cost

*Gordon, R. *F. Rabelais a la Faculté de Médicine de Montpellier. Autographes, documents et fac-similie.* (Montpellier & Paris, 1876).

was considerable, and Rabelais speaks of having to pay "the referendaries, proctors and such-like scribblers and blotters of parchment." He mentions in a later letter that he had made an end to his business, and it had cost him no more than the taking out of the bulls, "his Holiness having of his own good nature given me the composition." He believed that he had obtained nothing by the bulls but what was just and lawful.

Death of James Ballard

The sudden death of the Director of the Library on May 15, 1955, was a staggering blow. He had been connected for so many years with the Boston Medical Library that he was regarded by many as the Library itself. Sixty years of close association with physicians who acted as trustees and librarians, custodian of the treasures, deviser of a widely used classification for medical books, builder of the major portion of our collection, including the very complete files of periodicals, supervisor in the last two decades of the development of the historical collection, particularly the acquisition of manuscripts and incunabula, as well as all books on the history of medicine, especially New England medicine, Mr. Ballard stood out as the dean of the medical librarians in this country, greatly admired by many and looked up to for his progressive leadership and his kindness to junior members of his profession. In spite of all his interest in historical matters and old books he was primarily a medical librarian, perhaps the best trained of any man in this country, and it is a great tribute to him that when he died the Library was able to carry on at its usual pace without interruption of services, so well had he trained the small band of workers who are responsible for the day-by-day work that makes the Library such an important factor in Boston and New England medicine. Nothing would have pleased him more than to know that the principles of service that he incorporated into the Boston Medical Library served the Library well after he had left his post. Many tributes to him have appeared in the medical literature.

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MEDICAL PROGRESS

ALLERGY (Concluded)*

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The Steroids

The introduction and increasingly widespread use of ACTH and the adrenocortical steroids have provided a fascinating and provocative development in clinical allergy. The influence of these agents on allergic symptomatology has called increasing attention to the allergic diseases, not only by the laity but also by various branches of the medical profession. For example, the patient, who has been on prolonged hormonal therapy and who is facing an operation, is a problem for the surgeon as well as the internist.

The choice of available preparations is wide and is very likely to increase. ACTH is available for intravenous or intramuscular administration. Four preparations — cortisone, hydrocortisone, prednisone and prednisolone — are now used. All are effective

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orally, and the intravenous preparations of hydrocortisone and prednisolone have proved their worth. Hydrocortisone and prednisolone have been effective in ointments and lotions for local application in such conditions as atopic eczema and contact dermatitis. The question naturally arises which compound should be used since everyone would prefer to use the safest one. Unfortunately, all of them are capable of causing serious side reactions. None are any safer than the others. Commercially available ACTH has two disadvantages. In the first place, all such preparations contain some foreign protein, and the possibility of allergic reactions therefore exists; indeed, such reactions[81-83] have been reported. Secondly, ACTH must be given by injection.

All these compounds will suppress the symptoms of allergic disease if employed in proper dosage. None of the agents, however, permanently alter the over-all course of the allergic disorders. Repeatedly, it has been demonstrated that symptoms recur with, or shortly after, withdrawal. These agents are but newer forms of symptomatic therapy.

Because of the potential dangerous side effects the decision to use or not to use any of these agents must be made individually for each patient. Is the disease to be treated serious enough to warrant the risk? This is the important question to be answered in each patient.

Side Reactions

Mild side reactions such as weight gain, with abnormal increase in fat in the abdominal, supraclavicular and lower cervical areas, rounded facial contours and facial rubor are frequently encountered but are usually of only moderate concern.

Serious Complications

Serious complications of steroid therapy include osteoporosis, growth inhibition, hypertension, psychosis, vascular disease, which frequently occurs in the form of intestinal bleeding, masking and acceleration of infection and, in late cases, protein depletion. Among 43 unpublished cases of spontaneous hyperadrenocorticism or Cushing's syndrome studied by Dr. Fuller Albright and his group at the Massachusetts General Hospital, osteoporosis, the commonest serious symptom, was present in 39. Eisenhardt and Thompson[84] reported it in 53 of their 61 cases. If the daily dose of cortisone required for suppression of severe asthma of the intractable type is, as Norymberski, Stubbs and West[85] estimate, two or three times the normal rate of secretion of cortisonelike hormone, it seems logical that at least some of these complications should be anticipated in the face of prolonged steroid therapy. Recent reports have indicated this assumption to be correct.[86-89] In a series of 30 patients with intractable asthma maintained essentially free from asthma by two of these authors for periods up to six years on corticosteroids, 3 have demonstrated multiple vertebral fractures. One of these has had, in addition, a severe hemorrhage from a duodenal ulcer that necessitated gastrectomy. This patient subsequently died suddenly after massive masked bronchopneumonia, thereby demonstrating in 1 person three serious complications attributed to steroid therapy.

Difficulty of Withdrawal

Withdrawal of steroids in patients on maintenance therapy often presents difficulties, particularly after prolonged administration. Nineteen of the patients noted above were hospitalized after a year or more of such treatment for the purpose of abrupt withdrawal and, simultaneously, for comparison of calcium metabolism with and without steroid therapy in relation to potential osteoporosis. Abrupt discontinuance of steroid therapy[87] was chosen because previous experience had indicated that gradual withdrawal of the drug had resulted in exacerbation of asthma in most cases before therapy was entirely withdrawn. Twenty-four hours after withdrawal, headache, nausea, vomiting, restlessness and muscle or joint pains developed in nearly all patients. These symptoms subsided spontaneously after two to five days. The cause of this syndrome was not determined. It is of further interest that daily steroid therapy had to be resumed in all 19 patients within a few days to a few weeks because of the return of severe asthma, in spite of serious efforts to withhold these agents. Discontinuance of steroid therapy for even milder symptoms also had its problems. Such a withdrawal often recalls the words of the old song, "How you gonna keep 'em down on the farm, after they've seen Paree?"

These observations — namely, the transient, symptomatic type of action of the steroids, their dangers in prolonged treatment and the difficulty of their withdrawal — are made here to emphasize several important points. The first is the advisability of ensuring that the agents are employed only after every effort has been expended to make an etiologic diagnosis and to carry out a well conceived program of allergic management. Too often in allergy, symptomatic or suppressive therapy replaces rather than supplements well established procedures of investigation and treatment.

Selection of Patients for Steroid Therapy

The next rule of thumb is to employ these agents only after older, routine methods of treatment have failed. Many patients with varying manifestations of allergy were satisfactorily handled before the appearance of these hormones, and this is still true. The ephedrine preparations, potassium iodide, epinephrine, aminophylline and the antihistamines, coupled with understanding guidance, will still provide relief in a majority of cases.

In selected cases, the steroids are of great value. In fulminating acute allergic states such as status asthmaticus, or in severe serum disease, unresponsive to routine measures, these hormones will usually control the situation, with no necessity for prolonged therapy once the emergency is past. The action of the steroids is not sufficiently rapid to be effective, however, against the anaphylactic type of reaction that occasionally occurs within minutes to a few hours in highly sensitive persons after administration of a few allergens such as horse serum and penicillin. Here, epinephrine either subcutaneously or intravenously is the drug of choice. In other situations, it may be necessary to protect the patient over a given period until he is no longer exposed to allergens that cause his symptoms. Pollen asthma is a good example of this. Here, the patient with ragweed asthma may be saved from several weeks of hospitalization or loss of work in the fall by adequate steroid therapy when other methods such as pollen hyposensitization have failed. Steroid therapy can then be discontinued with no recurrence of symptoms as soon as ragweed is no longer in the air. Short courses of treatment limited to a few weeks or months with customary doses are seldom attended with serious complications.

The problem of selection of patients for prolonged maintenance therapy is more difficult. Here, familiarity with the symptom pattern, rather than the severity of a given attack, is the keynote. The persistence of symptoms, the length of remissions if any and the ability to obtain and to hold a job, to support a family or to maintain one by running the home are all determining factors.

Under certain circumstances, there are no absolute contraindications to the employment of these agents. The patient with a demonstrated duodenal ulcer, evidence of osteoporosis or old tuberculosis may have to assume the calculated risk of steroid therapy if failure to control his asthma presents an even greater risk to life or the ability to tolerate it. In short, prolonged steroid therapy is warranted only in cases in which the evidence in favor of chronic disability without such treatment outweighs the possibility of serious complications from the treatment itself.

Dosage

If these hormones are chosen as therapeutic agents, what principles have been found important in dosage? The initial total daily dose of whatever preparation is used must be adequate in amount, and administration sufficiently prolonged to suppress symptoms completely.[88,90] This rule is essential for adequate "bailing out" of the acute attack as well as a prelude to successful maintenance. Infraction of this rule is the most commonly encountered reason for failure in either short or prolonged therapy. By "failure" is meant failure to render and to keep the patient completely free or as nearly free as possible from all symptoms of asthma. For example, Mrs. B.B. was introduced to cortisone therapy for the first time in 1953, nine months before her original appearance at the Massachusetts General Hospital and three years after onset of intractable asthma. The original daily dosage schedule started with 200 mg. for the first twenty-four hours and was then reduced on subsequent days to 175 mg., 150 mg., 125 mg., 100 mg. and 75 mg., before the start of a maintenance dose of 50 mg. daily. On this program, her asthma was definitely improved, but at no time was it completely suppressed. In the next nine months she remained on 50 mg. of cortisone daily but was never really comfortable owing to varying degrees of wheezing. Moreover, she required two hospitalizations for severe asthma in her home city. She arrived at the Massachusetts General Hospital in status asthmaticus and required 200 mg. of cortisone daily for fourteen days before becoming entirely symptom free. During the past two years she has been followed closely by one of us and has been maintained clear of asthma on 50 mg. daily, the same daily dose that proved ineffective for maintenance after inadequate initial dosage at the onset of treatment with cortisone.

A criterion of complete suppression of symptoms as a guide to cortisone dosage has many advantages. Chief among these from the patient's standpoint is the restoration to normal or nearly normal health throughout therapy, a situation much appreciated by one who has previously experienced prolonged invalidism. An additional asset is the constant presence or absence of both subjective and objective evidence of symptomatology as a yardstick upon which the physician may base his optimum dosage level and upon which he may also compare the effectiveness of one preparation with another to his patient's advantage.

In view of increasing evidence of the late effects of cortisone, consideration must be given to those[91] who recommend that, in chronic asthma, a reasonable degree of relief by a relatively small dose of this hormone, supplemented by other medication, may be preferable to the complete control of symptoms by steroids alone. Before this important problem can be settled, however, it must be proved that small doses of steroid are of real use. If patients with mild symptoms are given small doses and mild symptoms are still present, it may be wondered whether there is any substantial benefit and if such a modified dosage schedule justifies the potential dangers and expense.

There is considerable evidence that gonadal hormones (androgen or estrogen, or both) have anabolic effects as stimulators of protein and osseous tissue, even in the presence of an excess of corticoid activity, and that they do not interfere with beneficial corticoid actions.[92] Although it will be several years before the effectiveness of such therapy can be evaluated, there is reason to believe that anabolic

steroids should be administered to protect the protein and osseous tissues in patients who are being given corticoid therapy, or even moderate "physiologic" amounts of corticoids when endogenous anabolic hormone levels are low.

A workable schedule for initial therapy covering cortisone and hydrocortisone for adults consists of 75 mg. every six hours for twenty-four hours and then 50 mg. every six hours until complete suppression of symptoms occurs. If maintenance therapy is to follow, the daily dose is reduced step-fashion at weekly intervals until symptoms begin to reappear. It is then established at 12.5 or 25 mg. above this level. Total dosage required for initial and daily dosage for maintenance therapy varies with each patient, but once the maintenance dose is established, it is remarkably consistent in the absence of respiratory infection and stress.

Indications of infection demand serious consideration in patients on cortisone therapy in view of the tendency of steroids to mask infectious manifestations or to accelerate them. Infection should be handled on established principles with antibiotics when indicated. The reappearance of severe asthma, which often accompanies this complication, is usually retarded by a temporary increase in daily cortisone dosage.

Another frequent cause of breakthrough in maintenance therapy and subsequent failure to control the recurrent asthma is reduction of the daily dose by design or by accident below the patient's customary tolerance level. If the daily dosage level is raised promptly before the symptoms become severe, a small increase in daily dose for a few days should be sufficient to suppress the outbreak. If asthma is allowed to assume severe proportions, however, return to large daily doses may be required.

Prednisone and prednisolone are more potent, milligram for milligram, than cortisone and hydrocortisone, and their dosages are therefore correspondingly lower. Dosages, as with the older steroids, must be determined individually. It appears that prednisone and prednisolone may be substituted for one another in comparable doses with similar clinical and metabolic effect. Most important is the observation that the administration of prednisone and prednisolone carries the same metabolic dangers as that of other corticosteroids.

Surgical emergencies and serious accidents are no longer rare occurrences in patients on maintenance steroids. Every patient on this medication, therefore, should be instructed to report this fact to any attending physician in the event of such emergencies and to carry a card in his wallet to this effect so that the steroid therapy may not only be continued but also increased temporarily when normal adrenal response may be so necessary but yet is impossible. Here, 100 mg. of hydrocortisone given in 1000 ml. of 5 per cent glucose in water as a slow intravenous drip (40 drops per minute) may be started an hour or two before and continued throughout and after the operation. This procedure can be repeated at twelve-hour intervals for the following twenty-four hours, or until the patient may be returned to his regular maintenance dose by mouth, or, if preferred, by the intramuscular route until oral medication seems advisable.

No overemphasis can be placed upon the necessity for the patient to keep in close contact with the physician throughout the whole of steroid therapy, no matter what its duration. This includes a considerable amount of guidance on the doctor's part, especially if prolonged maintenance is involved. When symptoms are first dramatically suppressed the physician is in a position to take the patient into his confidence and to obtain his co-operation. It is then that the rules should be laid down, and the reasons for them explained. A continuous written record of daily dosage by the patient will save much time. The daily dose should never be changed and much less omitted without consent. Any unexpected symptom should be reported and investigated immediately, for it may indicate the onset of a complication or the necessity for a change in steroid dosage.

Consideration of these details demands that the patient see the physician at least once a month and more frequently when indicated. Every patient with intractable asthma on maintenance steroid therapy must learn to appreciate that the price he must pay for return to a nearly normal status in life is one of maximum co-operation with his physician, whose duty, in return, is to do his best to keep his patient out of trouble.

Psyche and Allergy

A perennial question addressed to the allergist by both patients and other physicians is, What is the role of the psychiatrist in allergy? In a paper entitled "Psyche and Allergy," Wittkower[93] has called attention to the general disharmony between psychiatrists and somaticists in the field of allergy. Three reasons are offered for such disharmony — "ignorance, prejudice, and technical jargon." In a review of the literature it has been difficult at times to know whether or not the author's explanation or point of view has been grasped because of the technical jargon.

Wittkower offers the following comments in support of psychologic factors in allergic diseases:

> (1) the inadequacy of immunological findings in some patients suffering from allergic disorders [There is merit in the author's point of view, which suggests that present-day procedures may not be refined enough to demonstrate allergic factors in every case; although such allergic factors may exist, it is probable that other factors may be operative — one such factor may be the psyche.]
>
> (2) the precipitation of the onset of allergic disorders, of their relapses, and of individual attacks by emotional disturbance [Some evidence for this is presented in a paper by Miller and Baruch[94] reviewed below; certainly,

sporadic attacks induced by emotional disturbances do occur, but it is difficult to accept the notion that the disease is induced completely by psychologic traumas.]

(3) the similarity in personality structure of patients suffering from allergic disorders. . . Asthmatics have in common a deep-seated emotional insecurity and an intense need for parental love and protection. [There is no need to deny the existence of the similarity of personality structures, but the question is raised whether this is the result of the disease rather than a precipitating factor.]

(5) interchangeability of allergic disorders with gross psychiatric disorders. [Reference is made to low (reported) incidence of asthma in mental institutions; doubt is expressed if the hospital environment alone, relatively free as it is of extrinsic allergens, could account for the very low incidence.]

The author concludes that patients suffering from allergic disorders can be divided into three groups:

1. Pure organic allergy.
2. Pure psychiatric.
3. Combination of specific hypersensitivity and specific emotional states.

Detweiler[95] considers psychogenic factors one of a group of "trigger pullers." He emphasizes a point with which there is much agreement but that has been lost sight of by some — namely, that the capacity to react (in the patient with asthma, a capacity for bronchial spasm), either inherited or acquired, must be present before psychogenic impulses will result in an allergic response. Asthma has not been induced by any method in man except for potentially "atopic" persons.

In a psychologic study of 90 allergic children, Miller and Baruch[94] elicited a history of traumatic (psychologic trauma) incidents in 68 children before the first onset of allergic symptoms. The largest number, 22, seemed to result from the loss or threatened loss of a parent. The second largest group involved marital conflict within the family. Other causes included death, birth of a sibling, physical violence and surgery.

Attention is called to the fact that this sort of incident occurs in some form or other in the life of many children without eliciting any difficulty. "That severe physical illness should have followed in the group can be explained only on the basis that the seed must have fallen on fertile soil — a soil prepared both allergically and psychologically."

In a study of 22 allergic children, Mitchell et al.[96] inquired into the mother-child relation. They were impressed by the capability and competence of these mothers. They "ran" the family and were generally the dominant person in the home. "An underlying attitude of rejection either conscious or unconscious could be readily discerned." The mothers' feelings oscillated between outright or concealed hate to one of utmost concern and solicitude. This periodic oscillation seemed significant to the authors, who observe that most allergic children run a somewhat periodical course. They offer a psychologic hypothesis in which these mothers find themselves frustrated. The basis for this frustration need not be of concern. Certain needs, however, arise, for an outlet to this frustration, and for some reason attention is centered on the child, who does not supply any gratification for the mother but rather leads her to an increasing state of frustration. In seeking other solutions for her feelings she, "in desperation," considers the child responsible for her state of affairs. Threatened and annoyed she reacts with an attitude of pushing away and rejecting the child. The child experiences anxiety and fear of losing his mother's love:

> Ordinarily when a child feels insecure (in such a situation) he becomes resentful and shows it by word and behavior. But it is characteristic of the allergic child that he is unable to bring his resentment out by word and behavior. He characteristically blocks the outgoing expression of his resentment and turns it on himself. He expresses it by using his allergic constitution.

The suggestion is made that "subclinical allergy when combined with subclinical psychologic factors produces the picture of the manifest allergy." This psychologic factor is the fear of losing the mother's love.

Bakwin[97] stresses the point that anything that upsets the child or makes him unhappy may be the straw that tips the scale and brings on an (allergic) attack. Attention is called again to the mother-child relation. A dominating mother may elicit either submission or rebellion from her children. If the former, a child may substitute a physical condition for his pent-up emotional problem — for example, an attack of asthma. Thus, a child who is allergic and has already an established pattern of behavior as a result of antigen-antibody reaction may find this behavior elicited by a tension-producing situation. If he cannot openly rebel, he must submit, and thereupon substitutes an attack of asthma.

Abramson[98] believes, from his studies, that the allergic child is not primarily rejected, but rather that the opposite may occur — mutual engulfment (introjection). These parents desire to have their children develop in their own image of what their children should be. Attempts are made to coerce the developing child into a pattern consistent with parental ideas of what the boy or girl should be. The child, handicapped by eczema, or asthma, is forced into a distorted state of dependency. The development of independence and maturity is constantly threatened by the engulfing parent. The allergic child will more often submit, but resolves his anger or rebellion by having an allergic attack.

Miller and Baruch[99] studied the hostility pattern in a group of allergic children. In general, hostility in children presents itself objectively in four patterns: direct (outspoken hostility toward parents); indirect (bed-wetting, whining behavior and food refusal); displacement (teasing other children and cruelty to animals); and hostility turned against self (hair pulling, nail biting, head banging and accident proneness). The nonallergic child manifests his hos-

tility in an outward-directed manner in a significantly higher proportion of cases. Hostility against self is more common in allergic children.

On the experimental side, the following seems to merit comment. Wolf et al.[100] report on the effect of noxious stimuli on the nasal mucosa in an attempt to demonstrate the concept (Selye and others) that "disease processes occur as biologic patterns of defense set in motion by a variety of specific and nonspecific threats to the integrity of the organism." After a base line of nasal function had been established, subjects were exposed to a series of graded threats beginning with those directed specifically at the nasorespiratory passages. Ammonium carbonate produced an expected reaction characterized by hyperemia, swelling of nasal structures, hypersecretion and obstruction. Similar responses were produced in turn by pollens and pain and finally by word symbols in terms of frustrating material uncovered in the course of psychiatric interviews. It is inferred from such experiments that "functional changes with associated troublesome symptoms may be the end stage of psychosomatic processes set in motion by life experiences which, like allergens, have an especially noxious significance for the host." These studies were extended[101] to demonstrate that a life situation engendering conflict and anxiety enhances the intensity of the symptoms of rhinitis and the magnitude of mucous-membrane response already present in sensitive subjects and, secondly, enhances the response of the nasal tissues to an additional assault by pollen.

Funkenstein,[102] intrigued by the low incidence of asthma among patients in mental hospitals (he quotes Leavitt's figure of 0.08 per cent in a survey of 11,647 patients with functional psychoses) and the fact that the majority of asthmatic patients in whom psychoses or other mental disease develop are free of asthma during the disease, attempted to ascertain what changes in the patient's autonomic reactions accompanying the psychoses could account for absence of asthma at that time. Normally, an intravenous injection of epinephrine produces a sharp rise in blood pressure and a precipitous drop in a short time (adrenergic stimulus). An intramuscular injection of methacholine (Mecholyl) produces a gradually diminishing blood pressure and subsequently a slight rise above the normal. In a patient with asthma an attack is induced. After development of a psychosis Mecholyl caused a drop in blood pressure for a brief time and an associated brief asthmatic attack. When the patient recovered from her psychosis, the drug produced a long-sustained attack of asthma. The development of the psychosis was accompanied by a marked increase in sympathetic-nervous-system reaction, which was manifested in the test situation as a rapid recovery from the parasympathetic effects of Mecholyl.

In further experiments along these lines, Funkenstein[103] found that during psychologic stress Mecholyl usually produced milder and shorter asthmatic attacks than when the drug was given to the same patient during a nonstress period. Cardiovascular measurements made before and during stress suggest that excessive secretion of nor-epinephrine-like or epinephrine-like substances during stress could account for absence or mildness of the asthmatic attack precipitated by Mecholyl.

In a "Psychosomatic Study of Infantile Eczema," Rosenthal[104] offers the thesis that eczema arises in certain predisposed infants because they fail to obtain from their mothers or mother substitutes adequate soothing physical contact (caressing and cuddling). "Comparisons of findings in interviews with the mothers of twenty-five infants with infantile eczema and of eighteen control cases revealed that in a significantly higher proportion among the eczema cases the mother tended to let the baby cry without picking it up unless there was some obvious physical discomfort present in the infant." The author states that "there was good evidence . . . that the inadequate handling of the infant had preceded rather than followed the onset of the rash." This is important, for it is understandable that after the appearance of the rash the infant may appear repugnant to the mother and this may be responsible for the decreased handling of the child. It has been thought that this situation may well be responsible for the persistence of the disease beyond the usual eighteen to twenty-four months in certain cases. It is difficult with the data presented to know what were the criteria for diagnosis except that it be made by a "competent pediatrician or dermatologist." One would like to know about the other criteria for allergy — family history, relation to diet and so forth. The author, however, recognizes these possibilities, for in his summary he states, "other factors such as constitutional predisposition and allergy were possibly equally important." Drawing analogy from the general inability to induce asthma except in atopic persons, one would expect that if lack of physical contact were responsible for eczema, it could only be in the constitutionally predisposed patient.

Prophylaxis

This subject has not received much attention except as a secondary consideration in the treatment of the patient who is known to be allergic. Shulman,[105] in 1948, stated, "The inheritance of the tendency to develop allergy is now generally accepted." On this basis he selected the "potentially allergic" infant and proposed to prevent or minimize the occurrence of allergic disease by controlling the external and internal (that is, food) environment. Avoidance of animal emanations and dust-free precautions were recommended. Substitutes for or

avoidance of the five basic foods used in infant feeding (that is, milk, egg, wheat, orange juice and fish — fish-oils) were advised. No statistical study was presented. Indeed, Shulman concluded, "Since the study of inheritance is so complicated, reports of individual cases successfully avoiding allergic manifestations can neither refute nor support the aim of the proposed regime for allergic prophylaxis." McGee[106] recommended a similar approach, believing that one can modify or prevent allergic disorders in potentially allergic children — that is, children born into families with members who are known to be allergic.

Glaser and Johnstone[107,108] have reported a diminution in the occurrence of allergy in infants fed cow's-milk substitutes from birth. Drawing analogy from the clinical observation that infants unable to tolerate egg yolk at three months do so at nine to twelve months, the authors hoped to overcome milk sensitivity by withholding milk. In the course of their study they noted over a period of years (ranging from one to ten) that there appeared to be a marked decrease in the incidence of major allergies in children fed in this way. The assumption was that when hypersensitivity to milk or other potent allergen occurs, other allergies more readily develop. The statistical method employed has been criticized by Lowell and Schiller.[109] Hill[110] calls attention to the possible hazards of soybean foods used in this way and points up the overemphasis on milk-free infant foods often used "in many situations having nothing whatever to do with milk allergy."

In a recent communication Ratner and Silberman[111] have questioned the hereditary aspect of allergy. This would deal a severe blow to all prophylactic procedures based on the potentially allergic child since the selection of this "child" depends on the presence of a positive family history.

There is no disagreement that withholding or avoidance of a particular antigen would prevent symptoms from that antigen. The concept, however, that such an omission will prevent later allergies requires study. Data to date are incomplete and are not convincing.

Conclusions

During the past five years progress in allergy has not been remarkable. Theories of antigen-antibody reaction, site of antibody production and types of antibody remain controversial. The increase in use of drugs has led to an increased number of allergic reactions. The promise of a new era by the steroids has not been fulfilled. True, there is now a reliable method of bringing relief to those with allergic symptoms, but steroids are not fast enough in anaphylactoid reactions and prolonged use is fraught with danger. Psychiatry promised much, but clarity has been lacking. During the past five years, however, interest and organization have augmented research, both basic and clinical, which should solve at least some of the outlined problems.

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MEDICAL INTELLIGENCE

COMBINED ERYTHROID HYPOPLASIA AND SYMPTOMATIC HEMOLYTIC ANEMIA

Report of a Case

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WHITE RIVER JUNCTION, VERMONT

THE simultaneous occurrence of pure erythroid hypoplasia and symptomatic hemolytic anemia is sufficiently unusual to justify the case report presented below. In a review of the literature only 2 such cases have been found, and the occurrence of this combination as a manifestation of Hodgkin's disease is apparently unique.

CASE REPORT

C.M., a 63-year-old Lithuanian lumberjack, was admitted to the hospital for the 1st time on January 4, 1955, in circulatory collapse. He had apparently been well about 5 months previously, when he noted the gradual onset of weakness, lethargy and generalized body pain. He had sought no medical attention until the day of admission, when he complained of profound weakness and shortness of breath.

Physical examination showed a confused, weak man with slight yellowing of the scleras. A systolic murmur could be heard over the entire precordium, and a diastolic gallop at the apex. The lungs were clear. A firm liver edge was felt 3 cm. below the right costal margin, but the spleen could not be palpated. Generalized rubbery lymphadenopathy was present. Aside from a soft, nontender tumor, thought to be lipoma, over the anterior aspect of the left shoulder, the rest of the examination was not remarkable.

The temperature was 100.6°F., the pulse 112, and the respirations 34. The blood pressure was 70/50.

On the night of admission the hemoglobin was 5.5 gm. per 100 ml., the hematocrit 11 per cent, the red-cell count 1,150,000, and the white-cell count 10,400, with 72 per cent neutrophils, 23 per cent lymphocytes and 5 per cent monocytes. Autoagglutination made blood typing difficult. On smear the red cells appeared slightly microcytic and hypochromic. Platelets were abundant. A reticulocyte count was 0. A stool guaiac test was negative, and no red cells were present in the urine.

The patient was maintained throughout the night without transfusions. In the morning, after hydration, the hemoglobin had fallen to 2.1 gm. per 100 ml., and the red-cell count to 710,000. The serum bilirubin was 1.09 mg. per 100 ml. direct and 2.08 mg. total, and the urinary urobilinogen was positive in a dilution of 1:100. At that time transfusions were begun. Type O, Rh-negative blood with anti-A and anti-B substance was used exclusively. Throughout the next 21 days 9 liters of blood was administered.

Sternal-bone-marrow aspiration was done on the 4th hospital day. The specimen contained only a small amount of marrow and showed a marked reduction of erythropoiesis, with normal granulopoiesis and platelet formation. The serum albumin was 4.0 gm., and the serum globulin 4.6 gm. per 100 ml. A striking increase in the gamma-globulin fraction was shown by filter-paper electrophoresis.

Transfusions produced only a transient rise in hemoglobin (Fig. 1). Repeated examination of the stools and urine for blood were negative. The serum bilirubin and urinary urobilinogen remained persistently elevated. Lymph-node biopsy, 1 week after admission, was interpreted as consistent with malignant lymphoma of the Hodgkin type.

Cortisone was begun on the 11th hospital day. Five days later there was still no evidence of reticulocyte response. Despite continued transfusions the anemia remained severe. On the 17th hospital day 28.4 mg. of nitrogen mustard was given. On the same day, for the 1st time, a reticulocyte was seen in a count of 1000 red blood cells (0.1 per cent).

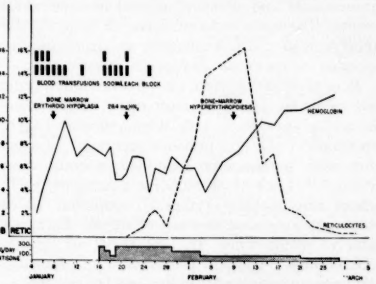

FIGURE 1. *Effect of Therapy on Erythroid Hypoplasia Combined with Symptomatic Hemolytic Anemia.*

At that point a steady reticulocyte response began, reaching a maximum of 16.4 per cent and being accompanied by a gradual rise in hemoglobin. The serum bilirubin and serum globulin fell to normal levels. Bone-marrow examination at the height of the reticulocyte response revealed hypererythropoiesis. A re-examination of serum proteins by electrophoresis showed normal values. The cortisone was gradually reduced and discontinued after 6 weeks (Fig. 1).

Five months after the 1st admission the patient was readmitted to the hospital for excision of the large tumor, which proved histologically to be a hibernoma. At that time the hemoglobin was 12.1 gm. per 100 ml., and the white-cell count 10,750, with 67 per cent neutrophils, 29 per cent lymphocytes, 2 per cent monocytes and 2 per cent basophils. The reticulocyte count was 1.3 per cent; the Coombs test was negative, and the serum bilirubin 0.13 mg. per 100 ml. direct and 0.51 mg. total. He was well except for persistent fatigue, and no further evidence of Hodgkin's disease had appeared.

DISCUSSION

Because of his desperate condition and unusual hematologic findings this patient presented several problems. Neither red-cell survival nor immunohematologic studies could be made, but the evidence for a hemolytic process seems convincing; 4500 ml. of whole blood given in six days resulted in but little rise in hemoglobin. The increased urinary urobilinogen, the increase in total bilirubin, the high gamma globulin and the autoagglutination all point to hemolytic disease, as does the return to normal values after treatment.

This patient was given both cortisone and nitrogen mustard. The response of acute hemolytic anemia to

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steroid therapy has been well documented.[1-4] Although it is widely accepted that nitrogen mustard acts to depress antibody formation, its use in hemolytic anemia has rarely been reported.[1,5] The urgency of the situation made it necessary to give nitrogen mustard before the full effect of the cortisone could be evaluated. Because of this the specific role of each drug in this case will never be known.

Reports of aplastic crises in congenital hemolytic jaundice[6-8] and sickle-cell anemia[9] have been frequent in the recent literature. These, however, are marked by true bone-marrow aplasia, with diminution in granulocytes and platelets as well as erythroid elements. The cases reported have, in general, shown spherocytosis and splenomegaly and have usually responded to cortisone therapy or splenectomy.

Pure erythroid aplasia, on the other hand, is much less common. It occurs most often in children.[10-12] In adults association with thymic tumors has been mentioned.[13] Only 2 previous reports of its association with autoimmune hemolytic anemia can be found.[14,15] Loeb et al.[14] discuss 2 brothers, each of whom had primary erythroid hypoplasia. In each there was a striking response to steroid therapy and later to splenectomy. In 1 of the 2 an associated autoimmune hemolytic process was mentioned. In the case reported by Eisemann and Dameshek[15] pure red-cell anemia was also associated with hemolytic anemia, which improved somewhat after ACTH and responded well to splenectomy.

The spleen in the patient described above could not be palpated despite persistent efforts. In the case presented by Eisemann and Dameshek[15] the spleen weighed 600 gm.; and in that of Loeb et al. (with hemolytic anemia) 650 gm. The brother (who had no evidence of hemolysis) had a spleen weighing 260 gm. Whether splenic inhibition of bone marrow is a factor in aregenerative anemia is still a moot question. Certainly, splenomegaly is usual in hemolytic disease — especially so in cases of long standing. It may well be that the patient discussed above had an acute process with a rapid remission and therefore a large spleen did not have time to develop. At present the spleen is still not palpable despite a persistent minimal anemia.

Summary

The simultaneous occurrence of autoimmune hemolytic anemia and pure red-cell aplasia has been reported but twice previously in the medical literature. A case of malignant lymphoma of the Hodgkin type with this combination is reported.

I am indebted to Dr. Ralph E. Miller, of the Department of Pathology at the Mary Hitchcock Memorial Hospital, Hanover, New Hampshire, and at the Veterans Administration Hospital, White River Junction, Vermont, for the interpretation of the pathological material in the case reported.

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CONCERNING ADULT EDUCATION

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In 1928 the published report on the extensive studies of adult learning by Thorndike et al.[1] at Columbia University gave spark to the interest in adult education that was then smoldering. Contemporaries in education and psychology have built the factual material from these scientific studies into their thinking. For the physician, too, there is much in this work on adult learning to challenge thought.

This authoritative report concludes that adults to the age of forty-five should expect to learn in much the same manner and at the same rate as they did in the late teens or early twenties and that age, itself, is a minor factor. "Capacity, interest, energy and time are the essentials." Also, "If we keep learning, we may expect to lose less of our ability to learn." At the New York Academy of Medicine, the Graduate Fortnight on Problems of Aging, Dr. Ross McFarland,[2] when considering "The Psychological Aspects," stated that recent evidence indicates that the period of maintained ability to learn can, more appropriately, be extended to the age of fifty or fifty-five years.

Adding of years to life takes time and so, at the termination of a physical examination, one prescribes to maintain the physical well-being, and still may dismiss the mental and emotional consideration of the patient with a suggestion for recreation, or a bit of advice on some interpersonal relation. It is known, however, that if there is to be long life and a

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good one, old age must have a share of financial security, some creative outlet, and a continued ability to accept change and sustain interest in community affairs — all of which can be fostered through earlier adult education.

The physician believes in adult education, as evidenced by continued study, but is not apt to stress its positive value to the patient. It seems that, by reason of their patients' needs, their own personal convictions and the over-all good to accrue, physicians should actively support the program of adult education, by helping to create both interest and demand. And in doing so, they should more frequently use the prescription of adult education now available.

Interest in determining the present offerings in adult education prompted a brief questionnaire to all state departments of education. Forty-three states replied without delay. Of these, 32 have adult-education programs at the state level: 6 are vocational only; the others have programs covering a wide range of interest. Nine states have good programs in the larger districts, conducted at a local level. Two states have little activity in this field and no data. Five reported a rapidly growing interest. The number of persons needed to create a class ranges from 6 to 15. The expense is relatively little or nothing. To show the scope of subjects considered for adult teaching, the following is taken from the 1955 *Manual on Adult Education* of the state of Minnesota:

> The range of topics and activities that make up the content of adult education is suggested in the following classification of subject matter in fourteen broad areas or fields together with examples of classes and activities in each area. It has been emphasized that the scope of adult education is as "wide as society and as varied as life." The following classification of areas and names of activities is for convenience only. *It is not the intention to delimit or formalize the content and program in any way.*

Academic
- Secondary school courses for credit
- College courses for credit

Civic and Public Affairs
- Government and national problems
- Citizenship
- Local government and problems
- Leadership training
- Civil Defense

Parent and Family Life
- Family and home relations
- Child and adolescent psychology
- Pre-marriage instruction
- Pre-school child laboratory
- Guidance of children's reading
- Use of television and radio by children

Americanization and Elementary Education
- Literacy
- Citizenship-training for foreign-born
- Preparation for naturalization

General
- Astromony for beginners
- Study of rocks and local rock formation
- Bringing science up to date
- Refresher Mathematics
- American Heritage discussion groups
- Short story writing
- Newspaper reporting and editing
- Languages — elementary and advanced. For business, travel, conversation, writing, and translating
- Practical psychology
- Personality development
- Public speaking
- Speech correction
- American history
- Historical background of world problems

Music and Drama
- Music appreciation
- Music theory
- Chorus — community
- Orchestra — community
- Band — community
- Men's chorus
- Women's chorus
- Chamber music groups
- Little theater groups
- Stagecraft

Arts and Crafts
- Metalcrafts
- Leathercrafts
- Making things from plastic
- Making things from wood
- Jewelry making
- Ceramics
- Weaving
- Silk screen process
- Painting — oil and watercolor
- Art and criticism
- Sketching
- Commercial art
- Design
- Photography

Agriculture
- Farm management
- Animal husbandry
- Dairy operation
- Farm welding

Business and Distributive
- Typewriting
- Shorthand
- Bookkeeping and accounting
- Business machines
- Business Law
- Federal and State regulations — income tax law
- Practical law
- Insurance — all types
- Retail selling
- Salesmanship
- Junior executive training
- Establishing and operating your own business

Activities for the Aged
- Preventive mental hygiene
- Handicrafts
- Social activities
- Retraining
- Civic interests
- Selected subjects and activities listed in other areas

Homemaking
- Nutrition
- Food — purchasing, preparation, canning, freezing
- Sewing — fundamentals
- Sewing — clothing, draperies, slip-covers, etc.
- Knitting and needlework
- Millinery
- Home planning — interior decoration, remodeling, lawn and shrubs, safety, etc.
- Home nursing
- Money management
- Consumer education

Trade and Industrial
- Automotive
- Electrical
- Machine
- Welding
- Building trades
- Home woodworking — furniture repair, upholstering, etc.
- Industrial arts
- Mechanical drawing
- Foremanship training

Physical Education, Health, and Safety
- Physical fitness and health for men
- Physical fitness and health for women
- First aid
- Swimming
- Auto driver training

Recreation
- Indoor recreational opportunities
- Outdoor recreational opportunities
- Sports
- Physical education
- Bridge
- Golf
- Dancing
- Square dancing

Colleges and junior colleges in every state have active adult programs and are interested equally in informal study and study for credit. Here, the cost is higher, of course, but it would decrease with increased enrollment and less need for advertising. The subject range can be almost unlimited.

In fact, when considering the subject of adult education, one soon gains the impression that a feast is prepared and that the guests are eagerly awaited. The physician may unhesitatingly whet the appetite without concern for intolerance or overload.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42291

PRESENTATION OF CASE

A twenty-five-year-old woman entered the hospital because of progressively increasing headaches, vomiting, "numbness" of the legs and trunk and episodic visual impairment.

Six weeks before admission, she gave birth to a normal infant after an uneventful pregnancy, during which she was generally well. Delivery was performed by cesarean section under spinal anesthesia because of a didelphic uterus. Upon awakening from the preanesthetic medication, she began having severe generalized headaches, described as beginning in the back of the neck and extending upward over the entire vertex. The headaches continued intermittently from that time onward, and on discharge from the hospital eight days after delivery she felt generally weak but was well otherwise.

About three weeks before admission, there was a sudden episode of incontinence of urine and feces, after which she had persistent urinary urgency and constipation. On at least two occasions speech abruptly became nasal, and she then became unable to speak for ten or fifteen minutes, without loss of consciousness or convulsive phenomena. Because of these symptoms, she entered a hospital, where neurologic examination on admission was unremarkable. Lumbar puncture yielded xanthochromic cerebrospinal fluid under an initial pressure equivalent to 50 mm. of water; the cerebrospinal fluid contained a protein of 288 mg. per 100 ml. and no cells; two subsequent lumbar punctures gave similar findings, except that the third "showed many cells, probably lymphocytes" and a pellicle.

Headaches, meanwhile, became progressively more severe, and nausea developed. One week before admission to this hospital she complained of the gradual development of "numbness" described as a "wooden" feeling, without prickling or tingling, of the legs, lower trunk and chest below the mid-sternum. On re-examination the deep reflexes in the arms were normal. Knee and ankle jerks were brisk, with clonus, and the plantar reflexes were bilaterally extensor. Over the following week she began having severe vomiting. In addition she had brief attacks, lasting about a minute, in which there was a whirring sound in the ears "like a sea shell," followed immediately by a feeling of "numbness," which was different from that which she previously experienced and which swept over her entire body, and decrease of vision, especially in the right eye; these symptoms were associated with great increase in the severity of the headache.

Two years before admission a vaginoplasty was performed under spinal anesthesia because of a double vagina. After this operation she had frequent "terrific headaches," which persisted intermittently from that time onward. The past history was otherwise noncontributory, and the family history was unremarkable.

Physical examination revealed that she was in some distress from headache and nausea but alert and co-operative, with intact sensorium. The general physical examination disclosed no noteworthy findings. On neurologic examination there was slight to moderate stiffness of the neck to forward flexion. The sense of smell was intact. Visual acuity was reduced to ability to read 3-inch capital letters with the right eye and to counting fingers with the left eye. By confrontation there was a large inferior temporal defect including the macular area on the right and a large central scotoma on the left. The optic fundi, pupils, and ocular movements were normal. The right corneal reflex was decreased, and there was sensory impairment to pinprick and light touch over the right cheek and possibly over the left as well. Jaw movements and other cranial-nerve functions were intact. The jaw jerk was not obtained. There was weakness of all four limbs, more pronounced distally than proximally, with flaccidity of the arms and spasticity of the legs; performance of skilled movements was commensurate with the degree of weakness. Deep reflexes were absent in the arms; patellar and Achilles reflexes were hyperactive bilaterally, with ankle clonus; abdominal reflexes were absent; the plantar reflex was bilaterally extensor. There was slight blunting of pain sensibility to pinpricks below the mid-sternum, but light touch was well perceived. Vibration and postural sense were normal in the hands; vibration sense was slightly reduced in the feet, and postural sense was severely impaired in the big toes.

The temperature was 99.0°F., the pulse 96, and the respirations 24. The blood pressure was 110 systolic, 80 diastolic.

The urine showed a specific gravity of 1.010 and gave a ++ test for albumin and a negative test for sugar and bile; the sediment contained occasional red

blood cells, 25 white cells and 35 epithelial cells per high-power field and gave a ++ test for bacteria. Examination of the blood revealed a white-cell count of 8200, with 61 per cent neutrophils, 35 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils; the platelets were normal on smear; the hemoglobin was 11 gm. per 100 ml. The blood sedimentation rate was 45 mm. in one hour. The total protein was 6.8 gm., the albumin 4.5 gm., the globulin 2.3 gm., and the nonprotein nitrogen 21 mg. per 100 ml.; the sodium was 142 milliequiv., the chloride 98 milliequiv., and the potassium 3.9 milliequiv. per liter. Roentgenograms of the cervical spine, skull and chest on admission showed no abnormalities. An electroencephalogram on the second hospital day showed an abnormal record without localizing phenomena, characterized by increased voltage and bilateral slow waves (3-4-5 per second) throughout all leads.

On the evening of the second hospital day, the patient had a severe exacerbation of headache, preceded by a sound "like a sea shell in the right ear"; the headache began on the right side of the head, rapidly became generalized, throbbed and felt "as if the head were trying to burst." Simultaneously with the development of the headache, she noticed paresthesia (tingling) of the middle and lower parts of the face on the right, including the inner side of the cheek and the right side of the tongue and hard palate. Over the ensuing hours, the headache became more severe, reaching a peak about midnight; during this time, she became "numb all over" and extremely weak, so that she was unable to move the legs and barely able to move the arms. She was nauseated, and vision became further impaired. By the next morning, headache had subsided considerably, and she was again able to move the limbs but was completely blind. When examined an hour or so after this, she was able to perceive hand movements with the right eye and to count fingers with the left eye. The pupils reacted to light, and the fundi were unchanged. Oscillatory movements of the eyes were seen on ophthalmoscopy, but no nystagmus or ocular paresis was observed on testing of ocular movements. Motor power in the limbs was approximately the same as on admission.

On the third hospital day, she had another transient episode of intense headache, nausea and generalized numbness and weakness, with total blindness, lasting about thirty minutes. Later in the day she had an attack of severe vomiting and lost consciousness for several minutes. An examination by an otologist on that day disclosed normal hearing and no evidence of ear disease.

During the fourth and fifth hospital days, four attempts at lumbar puncture were made, each by a different observer at different lumbar interspaces; on each occasion the needle tip was believed to be within the subarachnoid space, and the patient had shooting pains in one or the other or both legs, but no fluid was obtained except on one occasion, when one drop of cloudy acellular fluid was aspirated; a Gram stain revealed no organisms. On one occasion an attack of unconsciousness lasting about three minutes was observed by a nurse; the patient said that she was "blacking out," and screamed; then the eyes rolled upward and to the right, and the left arm jerked. By the eighth hospital day, she was feeling better, and there was improvement in all the neurologic findings, although all persisted and on subsequent days there was very little change. Cortisone, 75 mg. every six hours, was begun on the tenth hospital day. Three days later there was another attack of severe headache and loss of vision, during which she was seen by an ophthalmologist, who found her to be completely blind, with dilated pupils (5 mm.) that did not react to light. The fundi and ocular movements were unchanged. After about fifteen minutes the headache subsided; one or two minutes later, she was able to perceive light, and the pupils were weakly reactive to light. In another five minutes the headache had almost completely gone, and she could distinguish forms in the peripheral fields. There was a dense central scotoma bilaterally. Similar episodes occurred daily over the next two days. During this period, she had several attacks of unconsciousness, with upward deviation of the eyes, extension and pronation of arms and extension of legs, followed after a minute or so by brief jerks of the arms, and recovery of consciousness after another two or three minutes.

On the twentieth hospital day, after an unusually prolonged episode of unconsciousness, a right parietal burr hole was made at Keene's point, and ventricular drainage was established. The ventricular-fluid pressure was equivalent to over 600 mm. of water; the fluid was clear and colorless and contained 46 red cells and 1 lymphocyte per cubic millimeter and 2 mg. of protein per 100 ml. Air ventriculography showed moderate symmetrical dilatation of the lateral and third ventricles; the aqueduct and fourth ventricle were not visualized.

Subsequently, several operative attempts were made to drain the ventricular fluid into spaces outside the craniovertebral canal, including a catheter between the lateral ventricle and the spinal epidural space and, later, between the ventricle and the mastoid antrum. No lasting success was obtained with any of these. Cultures of ventricular fluid repeatedly showed no growth. Headaches, vomiting and attacks of unconsciousness continued much as before, and the abnormal neurologic findings persisted.

On the fifty-eighth hospital day, she was found dead.

Differential Diagnosis

Dr. Philip R. Dodge*: I think this case today is presented not so much as a problem of differential diagnosis as an example of an unfortunate, but fortunately rare, complication of spinal anesthesia. Headache after spinal anesthesia is very common and usually has the characteristics of a drainage headache,

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being aggravated when the patient sits up and improving or subsiding when he lies down. The relation of the headache to posture in the case under discussion is not mentioned, but since it did not clear up in a few days, I suppose that some other mechanism was at play.

The generalized weakness that appeared early in the course seems consistent with the postoperative state and has no specific neurologic significance.

After an interval of three weeks the next neurologic signs and symptoms occurred. The urinary urgency suggests a bladder of small capacity that was due to heightened suprasegmental activity. The incontinence could have been failure of voluntary sphincter control on this basis. It does not tell us at precisely what level the lesion was. The associated bowel symptoms exclude local bladder disease as a cause for this symptom. The loss of speech could have been related to several neurologic mechanisms, but the associated nasal speech indicates that the abnormality was probably of brain-stem origin. The absence of alteration of consciousness or related symptoms is consistent with this, rather than with a seizure of cerebral origin. The negative neurologic examination shortly thereafter supports the view that the difficulty was episodic at this point.

The cerebrospinal-fluid findings are interesting. The association of low spinal-fluid pressure, xanthochromia and high-protein content, without pleocytosis, is consistent with Froin's[1] syndrome. This is generally seen with spinal-fluid block and impaired cerebrospinal-fluid circulation. No comment is made about the response to jugular pressure. If this test had been made here, I suspect that there would have been evidence of block. The yellow color in this situation is due to bilirubin. One specimen contained cells, but the fact that the cells were not counted exactly and that the word "probable" is used in describing the type leaves me uncertain how carefully the fluid was examined. The pellicle reflects the high-protein content and was probably due to fibrinogen. A pellicle does not necessarily indicate tuberculosis, as is commonly believed.

A week before admission there was additional evidence of spinal-cord disease, with sensory signs in both legs and trunk and signs of bilateral pyramidal-tract disease in the legs. At this point, one would guess that the locus of involvement was in the upper thoracic cord. This would be in keeping with the level of loss of sensation and with the normal functioning of the arms.

Coincidental with the developing signs of brain-stem and spinal-cord dysfunction, the previously mentioned headaches were becoming more severe and were now associated with vomiting. That these signs were caused by heightened intracranial pressure is suggested by the brief, transient episodes of severe headache, dimness of vision bilaterally, roaring in the ears and the curious generalized numb feeling that "swept over the body." This type of symptom complex is fairly typical of what we call a "hydrocephalic crisis" and is seen characteristically in a situation in which there is intermittent obstruction of cerebrospinal-fluid flow, either at the interventricular foramens, aqueduct of Sylvius or foramens of exit of cerebrospinal fluid from the fourth ventricle into the spinal subarachnoid space or at the basal cisterns preventing the spinal fluid from passing up through the tentorium over the surface of the cerebrum for reabsorption. Here, the prominence of brain-stem signs suggests that obstruction was occurring at the foramens of Magendie and Luschka, the foramens of exit from the fourth ventricle into the subarachnoid space.

The so-called "terrific headaches" that the patient had for two years before admission are not described in sufficient detail for specific evaluation of the mechanism of their production. It is interesting, though, that they followed an operative procedure under spinal anesthesia. I shall come back to this later.

The initial examination at this hospital is of interest. The stiff neck on forward flexion suggests meningeal irritation, or alternatively could have been related to pressure changes in the posterior fossa, with crowding of structures at the foramen magnum.

The re-examination of vision indicates that in addition to the episodic blindness, structural disease of both optic nerves was present, producing diminished visual acuity and demonstrable field defects. In the absence of papilledema, it seems unlikely that increased intracranial pressure alone could account for this finding, and I shall have to conclude that another mechanism was responsible. The fifth-nerve involvement, with diminished corneal reflex and sensory change over the face, was further evidence of brain-stem or cranial-nerve disease.

By this time also, the level of spinal-cord disease was better established. The spastic paraplegia with flaccid weakness and absent tendon reflexes in the arms suggests a cervical-cord lesion. It must have been over several segments to account for the extent of areflexia. All the ascending tracts were involved to varying degrees and the mid-sternal sensory level, which had not risen when the cervical lesion developed, also suggests that the previous notion of a thoracic-cord lesion is correct.

Was the patient on catheter drainage at the time the specimen of urine was examined?

DR. BRIANT L. DECKER: Yes; she was.

DR. DODGE: The laboratory findings are indicative of a urinary-tract infection and are in keeping with the fact that she was on catheter drainage. The elevated sedimentation rate goes with this finding.

The electroencephalogram indicates a generalized disturbance of function and is not inconsistent with the heightened intracranial pressure that I believe was present.

During the hospital stay the episodes interpreted as "hydrocephalic crises" increased in frequency and

severity, and after one such episode the patient became totally blind. The attacks soon became associated with altered consciousness and symptoms and signs of decerebration. I doubt if the seizures during the course of this disease were the result of a discharging lesion of the cerebral cortex, but one or two of the episodes in which there was unilateral jerking of an arm may have represented a cortical seizure. In all probability the mechanism of production of some of these disorders with "hydrocephalic crises" due to intermittent block of the spinal fluid is marked distention of the ventricular system, with consequent compression of ascending and descending fiber tracts. Also, when the compression involves the region of the third ventricle it is reasonable to assume that consciousness may be altered. We are sometimes told that the diminution in vision that one sees in this condition is caused by pressure on the optic nerves from the bulging of the third ventricle. It is only fair to say, though, that most of these explanations are hypotheses and that the actual mechanism of production of symptoms with this particular syndrome have never been thoroughly worked out.

A most significant finding is that four unsuccessful attempts at lumbar puncture were made at different lumbar interspaces by different operators. The fact that the needle was in the subarachnoid space is, I think, attested to by the note that the procedure provoked radicular pain. The only interpretation that I have is that the subarachnoid space was obliterated at the selected levels. This was apparently the interpretation made by the physicians caring for the patient because they instituted cortisone therapy in a vain attempt to halt the process. I am certain that at this point they were not optimistic.

The finding of ventricular fluid under increased pressure and dilated lateral and third ventricles on the ventriculogram leaves no doubt about the presence of hydrocephalus. The absence of filling of the aqueduct and of the fourth ventricle might be taken as evidence of obstruction at the upper end of the aqueduct, but one would want to know how serious an attempt was made to fill the posterior part of the ventricular system.

All attempts to circumvent an obstruction to the ventricular system at the aqueduct or below were to no avail, and the patient died on the fifty-eighth hospital day.

In summary, I am faced with the diagnosis of a progressive neurologic disorder that crippled and killed a previously healthy woman within about three months. The clinical findings indicate that the disease produced a disorder of function of and damage to both optic nerves, cerebrum, diencephalic structures, brain stem, cranial nerves and spinal cord, at two levels at least. Moreover, the illness caused hydrocephalus and episodic attacks of excruciating headache, with a generalized disorder of sensation, motility, and occasionally with loss of consciousness — "hydrocephalic crises." There is also evidence that early in the course of the disease, spinal subarachnoid block existed and that in the later stages there was nearly total obliteration of the subarachnoid space in the lumbar region. Though a disseminated disease such as acute multiple sclerosis could produce widespread lesions at various levels of the neuraxis, it would not explain the hydrocephalus, spinal-fluid block and progressive obliteration of the lumbar subarachnoid space. This certainly means that disease of the leptomeninges was present and after considering all facets of this clinical problem, I find it difficult to understand this illness except as an example of a subacute progressive adhesive arachnoiditis. The cause in this case seems to be in some way related, as it often is, to the spinal anesthetic that was administered just before the onset of neurologic signs.

The pathologic process that I suspect Dr. Richardson will show us is a marked fibrous thickening of the leptomeninges about the cord, with adhesions to the cord and nerve roots; I suspect also that he will demonstrate scattered areas of softening of the cord, especially in the cervical and upper thoracic regions. This pathologic finding is usually thought to be related to obstruction of the flow of blood to the cord that results when the small blood vessels are enmeshed in the fibrous overgrowth of meninges. I think that he will demonstrate a similar thickening of leptomeninges, within the intracranial cavity predominantly about the base of the brain. I anticipate that the process had occluded the foramens of exit from the fourth ventricle into the subarachnoid space, though conceivably the obstruction was at the level of the basal cisterns preventing fluid from filtering upward above the tentorium.

To explain the dense visual loss in the absence of papilledema, I expect to see an arachnoiditis about the optic nerves. This, of course, would not explain the intermittent visual loss that was in some way related to the sudden increases in intraventricular pressure. Whether the latter mechanism could have been responsible for all visual symptoms I cannot be sure, but I think not.

I believe that the changes in the cerebral hemispheres are explained by hydrocephalus and doubt if there was much change over the superior surface of the brain.

The actual cause of the meningeal changes that follow spinal anesthesia are poorly understood. Occasionally, it may be related to a low-grade infectious process, to a fungus or to sarcoidosis, but this rarely proves to be the case. Current opinion is that the changes are in some way related to a direct toxic effect on the meninges by the anesthetic agent or to an individual sensitivity to this agent. In this regard it is interesting that in the case under discussion the patient had had a previous spinal anesthetic with intermittent headache after the procedure.

In a certain number of cases the reaction — the arachnoiditis — has been traced to the inadvertent injection into the lumbar sac of some toxic substance, such as phenol or other preservative in which the anesthetic solution has been kept before injection. Recently, for just this reason, there has been a move away from this method of sterilization, or when this method is used the sterilizing solution is colored so that the anesthetic solution will be likewise colored if a crack in the vial of anesthetic exists. Another contaminant that may lead to an arachnoiditis is the detergent solution used in the cleaning of glassware and needles for spinal anesthesia. There are several reported cases in which this seemed to be the cause.[2,3]

There are several features that disturb me about the mechanism of production of this most unfortunate complication. Why does the disease progress long after the injection occurred? Is it simply because the neurologic changes are secondary to the reparative process — to the marked fibrosis — that is in itself progressing, or is it due to a sensitivity phenomenon? Also, why is there at times an interval of weeks or months before symptoms of arachnoiditis develop? Finally, how often does this complication occur? It is exceedingly difficult to gather statistics from the literature. Estimates are made that it occurs as often as 1 in 1000 spinal anesthesias though this figure is almost certainly too high.

The neurologist who primarily deals with the complications of spinal anesthesia is inclined to be quite wary of it. Yet it is important that we see this problem in its proper perspective, for there is no question that spinal anesthesia has much to recommend it and that the incidence of this complication really must be low. I am told that there has never been a complication of this sort from spinal anesthesia given at this hospital, and Dripps and Vandam[4] found no case of progressive arachnoiditis in over 10,000 patients given spinal anesthetics. The patients, over 8000 of them, were followed for at least six months. Thus, I think the conclusion should be that every attempt must be made to improve the technics employed without condemning the method. At the same time we must attempt to find out why these reactions occur and how they provoke the crippling neurologic disease.

DR. JOACHIM S. GRAVENSTEIN: I think Dr. Dodge has covered the case completely. I have nothing to add except to say that we still use solutions to sterilize our ampoules. They are colored, however. One of our staff has reviewed the literature and has discussed this problem with members of other departments. There is no definite information about the best way to sterilize ampoules. It is worth while to say that every attempt should be made to avoid leaving traces of detergents in the needles and syringes.

DR. DAVID G. COGAN: I am the unnamed ophthalmologist who saw the patient go into coma. One of the most interesting things about her from our point of view was that she had no papilledema even during the great increase in intracranial pressure. That presumably was due, as Dr. Dodge suggested, to the formation of scar tissue in the meninges around the optic canal so that the space about the optic nerve was no longer continuous with the intracranial space.

An unusual finding compared with other postanesthetic ophthalmoplegias was the time of six weeks. In the patients whom I have seen with postanesthetic ophthalmoplegia the paralysis developed, as I recall, about two weeks after the anesthesia, and then it was usually a sixth-nerve paralysis.

The intermittent blindness seemed to coincide with the rise in the intraventricular pressure; therefore, I should assume that it was a result of pressure, either against the nerves (as has been shown in blindness from the increased intracranial pressure in other cases) or of the optic nerve against one of the pulsating arteries. I should predict that extensive adhesions were found around the exit of the optic nerve as it entered the optic foramen.

CLINICAL DIAGNOSIS

Adhesive arachnoiditis produced by spinal anesthesia.

DR. PHILIP R. DODGE'S DIAGNOSIS

Adhesive arachnoiditis, produced by spinal anesthesia.

ANATOMICAL DIAGNOSIS

Adhesive arachnoiditis, with hydrocephalus and myelomalacia, probably secondary to spinal anesthesia.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At autopsy the pertinent findings were all in the central nervous system. Dr. Richardson will tell us about them.

DR. EDWARD P. RICHARDSON, JR.: As Dr. Dodge predicted, the significant pathologic findings were those of a severe adhesive arachnoiditis involving the entire neuraxis. The entire spinal subarachnoid space was filled with bands and irregular masses of whitish, tough fibrous tissue, most dense in the thoracic and lumbosacral regions, and more extensive over the posterior aspect of the cord than anteriorly. These formed firm adhesions with the dura mater and with the cord itself (Fig. 1). The arachnoid at the base of the brain was similarly affected, resulting in occlusion of the foramens of the fourth ventricle and thickening of the arachnoid around the chiasm and optic nerves. The arachnoid over the convexities of the brain, by contrast, was scarcely, if at all, thickened. At the level of the cauda equina, the nerve roots were matted together by the fibrous-tissue adhesions, and the subarachnoid space was obliterated, so that it was obvious why it was impossible to obtain any spinal fluid by

lumbar puncture. The cerebral convolutions were flattened, and the ventricular system was considerably dilated.

On microscopical examination, the arachnoid adhesions were composed of dense, relatively acellular collagenous connective tissue within which there were a few scattered small collections of lymphocytes in the adventitia of blood vessels. Many of the small meningeal arteries showed striking changes. A considerable number of them showed extensive concentric thickening of the subendothelial connective tissue, with severe narrowing of the lumen, but with sparing of the internal elastic lamina and the media (Fig. 2). The adventitia of such arteries was thick and dense, and blended with the proliferated connective tissue of the arachnoid. The anterior spinal artery in the lower half of the cord was severely involved in this manner and in a section through the lower sacral cord, was partly occluded by an organizing thrombus. In other small arteries in the spinal subarachnoid space, the entire media appeared homogeneous and acellular, at

FIGURE 1. *Dorsal View of the Lower Cervical and Upper Thoracic Spinal Cord, Showing Thickened Arachnoid, with Adhesions.*

times suggesting liquefaction necrosis of the media (Fig. 3). In still other arteries, the entire wall was made up of dense collagenous tissue, with no remaining evidence of the smooth-muscle fibers of the media or of the internal elastic lamina. Occasionally, small arteries were encountered in which the entire lumen was obliterated by organized thrombus. Veins in general appeared to be less involved than the arteries, but frequently had thickened fibrous-tissue walls. The vascular changes corresponded in degree to the severity of the arachnoid proliferation, and were absent in the normal arachnoid over the convexities of the cerebral hemispheres. They closely resembled what has been recently described by Greenfield and his coworkers.[5] In the brain, there were no significant alterations, and there was no subependymal inflammation or proliferation. Extensive areas of necrosis were found in the white matter of the spinal cord, however,

FIGURE 2. *Photomicrograph (Elastic-Tissue Stain, Low Power), Showing Various Stages of Disease in the Small Arteries.*

Note the thickened intima and dense fibrous tissue of the adventitia in the vessel indicated by the arrow.

beginning as a narrow peripheral zone, most pronounced in the lateral columns, in the mid-cervical region, and becoming more widespread in the thoracic region, where, at the level of the eighth thoracic segment, the lesions extended deeply into the posterior and lateral columns (Fig. 4). These cord lesions are best explained on the basis of ischemia and infarction, resulting from the severe alterations in the small meningeal arteries of the cord.

The findings were so typical of those described in other fatal cases of adhesive arachnoiditis after spinal anesthesia that it is difficult to escape the conclusion that the anesthesia must have been responsible for these severe inflammatory and destructive lesions.

DR. CASTLEMAN: Dr. Kubik, do you have any comments?

DR. CHARLES S. KUBIK: Dr. Dodge spoke about the progression that takes place in these cases and the

delayed onset of symptoms. The severe symptoms were delayed in this case for some time and continued to progress, once they started, to the time the patient died. There was increasing paralysis and, in the cord, foci of degeneration that would be consistent with

FIGURE 3. *Small Meningeal Artery (High-Power, Hematoxylin and Eosin Stain).*
The media is homogeneous, sparsely cellular and of necrotic appearance. The endothelium and intima are intact.

infarction or degeneration resulting from an insufficient blood supply. Considering the obliterative nature of the changes in the blood vessels, I suppose it is possible that the ischemia had some part in the progression of symptoms. The fibrosis also seems to have progressed and in some of the levels was well advanced. I might even raise the question of a process resulting from the anesthetic given two years before admission, after which there were definite symptoms in the form of severe persistent headache. In one or more of the other cases of arachnoiditis after spinal anesthesia, there has been less severe reaction — from which the patient recovered. I think it unlikely that all these cases are the result of some contaminant such as a detergent. I do not believe we have seen anything like this after myelography, in which the same detergents are used for cleaning the apparatus, and the capsules containing the material injected into the subarachnoid space are sterilized in the same way as those that are used in spinal anesthesia. It is possible that fluid oozes into the ampoules, for the neck of the ampoule is quite thin, and the capsule is sometimes dropped into the solution, which could well result in a small crack. On one occasion we discovered some of the alcohol in the ampoule, — fortunately before it was injected, — but I believe that is a rare occurrence and that the cause of the adhesive arachnoiditis in cases such as the present one still has to be discovered. It is quite likely that there is a mild reaction from which the patient recovers in a large number of cases, as indicated by the severe headaches that some of these patients have — which apparently are not lumbar-puncture headaches because they occur while the patient is lying down.

DR. CASTLEMAN: Dr. Adams, do you have any comments?

DR. RAYMOND D. ADAMS: This is fortunately a rare accident, but I have seen more than 25 patients clinically. Very few of them died. I believe that this is only the fourth autopsy that we have had. It seems to me that the best explanation of this neurologic disorder is that it is a chemical cerebrospinal meningitis

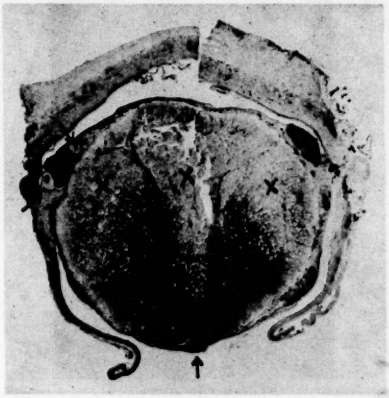

FIGURE 4. *Photomicrograph of the Spinal Cord (Myelin Stain, Low Power), Showing Destructive Changes in the White Matter of the Lateral and Posterior Columns (Indicated by X) and a Narrow Peripheral Zone Ventrally.*
Arrows indicate diseased arteries with thick walls. Note the greatly thickened meninges.

and that the chemical material may well be the detergent solution in which the ampoules are kept. The clinical effects of this are of two types: the most immediate effects, consisting in the milder cases of headache, stiffness of the neck, ophthalmoplegia and sometimes numbness of the cheek or loss of taste, and in the more severe cases, of headache, convulsions and cauda-equina syndrome with backache and paralysis of the bladder, bowel and legs. I think those effects are due to the direct action of the chemical on the

nerve roots, and they appear within a few hours or two or three days. In addition a delayed reaction develops some weeks to months after either the mild or the severe immediate reaction. Presumably, this is secondary to a protracted chemical meningitis and may take two clinical forms — a progressive constrictive myelopathy with spastic ataxic paraplegia and hydrocephalus. Our fatal cases have been the result of the latter complications. I think that the delayed reaction results from a constrictive fibrosis and vascular change in the meninges and not from direct action of the chemical material. Why should one assume that an exogenous toxin operates? In the first place, the nature of the pathologic findings suggests a chemical toxin. Moreover, Hurst,[6] in Australia, found that in animals the injection of some of the detergents used in anesthesiology caused a curious necrosis of the media of the meningeal arteries. Dr. J. G. Greenfield,[5] of the National Hospital, Queen Square, London, found a change in the media of the vessels similar to that in this human case of spinal-anesthesia meningitis. It is curious that both Hurst and Greenfield observed this vascular change at about the same time. I think Dr. Richardson has nicely demonstrated the vascular lesion in this case. The affected arteries are usually not occluded, and infarct necrosis has not been a part of the pathologic process in most cases.

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CASE 42292

Presentation of Case

A sixty-three-year-old man entered the hospital because of pain in the right arm.

Four months previously he noted the onset of gradually increasing pain in the distal third of the right arm. X-ray films were said to have shown Paget's disease of the right arm and skull. A course of radiation therapy was given, without relief of the pain. Demerol was required during the three weeks before admission. X-ray films taken a few days before entry were said to have shown a "cavity" in the right humerus. The insidious onset of hoarseness was noted about ten days before admission.

Anorexia and a weight loss of 20 pounds were noted during the two or three months before entry.

Physical examination showed a well nourished man with a hoarse voice. Laryngoscopic examination revealed paralysis of the left vocal cord. The muscles of the right shoulder and arm were atrophied. There was tenderness of the distal third of the right humerus. There were no enlarged lymph nodes. Examination of the chest and abdomen was negative.

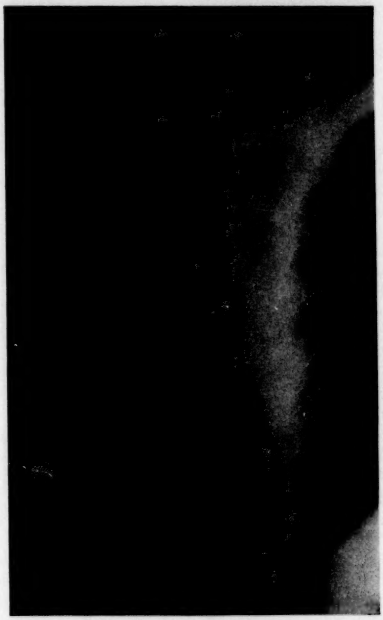

FIGURE 1. *Roentgenogram of the Proximal Half of the Right Humerus, Showing Extensive Paget Disease.*

The temperature was 98.2°F., the pulse 76, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100 ml. X-ray films of the right arm and forearm demonstrated extensive Paget disease of the entire humerus, more marked in the proximal portion (Fig. 1); in the distal end of the humerus an expansile lytic lesion measuring 4.5 cm. in diameter was present just above the condyle (Fig. 2); there was periosteal reaction opposite the defect, with marked thinning of the cortex; there was marked decalcification of the lateral humeral condyle. Definite growth of the lytic process was noted in comparison with films taken previously. Films of the chest showed an ill defined area of density in the left upper lobe of the lung superimposed

upon the first rib and apical area (Fig. 3); extending from this area toward the hilus were numerous linear shadows; the ductus node appeared enlarged; a diffuse mottling was seen in the lower portion of the

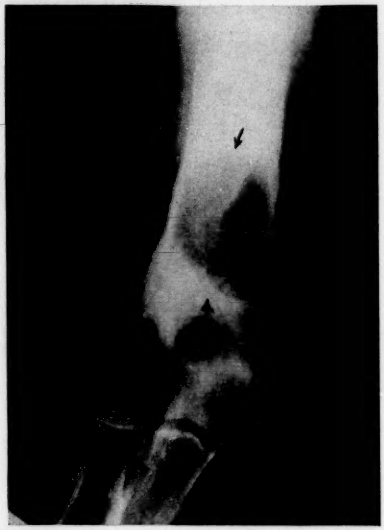

FIGURE 2. *Roentgenogram, Showing a Sharply Circumscribed Lytic Lesion in the Distal Portion of the Shaft of the Right Humerus.*

left-lung field; the heart was prominent in the region of the left ventricle, and the aorta was tortuous; paralysis of the left vocal cord was noted; the left pyriform sinus appeared normal; the right lung was normal. An intravenous pyelogram was normal except for early changes of Paget's disease seen in the bony pelvis.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM P. ROGERS, JR.*: This sixty-three-year-old man, with x-ray evidence of Paget's disease, had persistent pain and swelling of the right arm that was severe enough probably to produce atrophy of the muscles of the shoulder girdle, a paralyzed left vocal cord, a diffuse left apical pulmonary mass and apparently a mediastinal mass. Certainly, in any discussion of bone disease the clinician has to depend upon the interpretation of the radiologist; Dr. Hanelin, if you will help me now I shall be grateful.

DR. JOSEPH HANELIN: There is extensive Paget disease of the entire right humerus, more intense in the proximal portion (Fig. 1). In the distal portion of the shaft is the rarefied lesion that was described; it is purely lytic and is about 4 cm. in maximal dimension (Fig. 2). There is some periosteal reaction. The lateral condyle of the humerus is rarefied also; I cannot be sure that the rarefaction is the result of destruction; it may be caused by decalcification only. In a film made fifteen or sixteen days before the set taken on admission, the lesion is distinctly smaller so that it has grown rapidly in a little over two weeks. The abnormality in the chest is rather poorly defined and lies in the medial aspect of the left apex. There is thickening of the left hilus, with some nodularity at the margin. I doubt if the poorly defined densities in the left lower lobe are pertinent; they may be of long standing.

DR. ROGERS: Can you say with certainty that this was Paget's disease?

DR. HANELIN: Yes. The lesion involving the entire humerus is certainly Paget's disease.

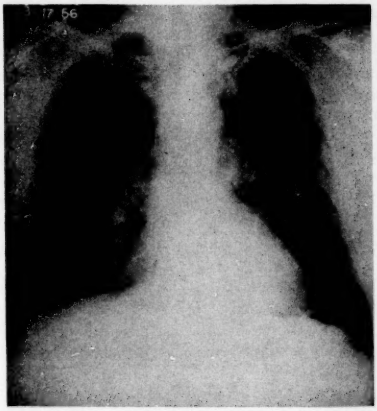

FIGURE 3. *Roentgenogram of the Chest, Showing a Poorly Defined Density in the Medial Inferior Aspect of the Left Apex (Upper Arrow), and Thickening of the Upper Portion of the Left Hilus (Lower Arrow).*

DR. ROGERS: We do not need the skull films.

DR. HANELIN: Even if there were no skull involvement that would still be Paget's disease. The changes are characteristic. Paget's disease may involve any bone in the body.

DR. ROGERS: Is the lesion in the pelvis more characteristic of metastases from the lung, thyroid gland or kidney or even from the breast or prostate?

DR. HANELIN: I do not think that I can be helpful. The primary lesion that occurs in an underlying Paget disease is sarcoma, which invariably is a lytic process not unlike this. The lesion in the humerus may not be primary; it could very well be metastatic from any of the regions that you have mentioned.

DR. ROGERS: Is there any reactive bone formation?

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DR. HANELIN: I do not think there is any bone formation per se within the tumor, although there is some periosteal reaction.

DR. ROGERS: Is the pulmonary lesion characteristic of tuberculosis? Is there evidence of cavity formation or is there just a clouding of the apex?

DR. HANELIN: I am unable to tell the nature of the apical density. It may be a new growth or infection. The combination of what appears to be adenopathy of the hilus and the density of the apex makes me think of primary carcinoma of the lung.

DR. ROGERS: That is the crux of the matter: can the whole series of events be explained by bone disease, or were there two separate primary conditions? I gather that the ventricular prominence was not important and that one cannot tell whether or not the patient had hypertension. We know that he did not have hypertension from the clinical record. Can you say whether there was possibly a metastatic deposit in the pericardium?

DR. HANELIN: I do not see any indication of metastases to the heart or pericardium.

DR. ROGERS: I shall not discuss that further.

The blood chemical levels and electrophoretic and urinary protein studies have doubtless been omitted from the protocol to avoid clouding the issue and to call my attention to the lesions demonstrated.

DR. BENJAMIN CASTLEMAN: They were not omitted; they were not done.

DR. ROGERS: The x-ray films are diagnostic of Paget's disease so that there is no point in discussing the lesions in the skull and the upper humerus. Paget's disease occurs in middle and later years and is often found on routine films without prior complaint from the patient. Usually, there is little or no alteration of general health; pathologic fractures are not frequent and when they do occur, are transverse as a rule. No fracture was demonstrated in the humerus in the case under discussion to explain the pain and the swelling.

In 10 to 25 per cent of patients with Paget's disease osteogenic sarcoma develops. This complication is more common in males, occurs chiefly during the decade between sixty and seventy years of age and appears in the sites already involved with Paget's disease. The prognosis regardless of treatment is more grave than when osteogenic sarcoma appears *de novo*. As in the case under discussion, the lesions are usually lytic and frequently show a periosteal reaction. In the space of two weeks this lesion showed growth. There was no clinical indication that it was metastatic from an occult primary tumor elsewhere, with the possible exception of the lung. Unfortunately, primary pulmonary tumors too often produce no symptoms until they are far advanced. The patient had no pulmonary symptoms despite the parenchymal and apparently mediastinal involvement. If the lesions had been bronchogenic carcinoma, one might have hoped to elicit a history of pain in the chest or hemoptysis by the time that the tumor had metastasized to the mediastinum or possibly to the humerus. Bronchogenic carcinoma metastatic to bone produces a lytic lesion, with little or no periosteal reaction and new bone formation.

My interpretation, on somewhat tenuous evidence, is that sarcoma developed in a previous site of Paget's disease, not demonstrated, in the lower end of the humerus and that it metastasized to the left upper lobe of the lung; from the lung secondary metastases to the ductus node probably occurred. Osteogenic sarcoma may metastasize to lymph nodes. Direct invasion of the left recurrent laryngeal nerve will produce vocal-cord paralysis. There were no cervical or laryngeal masses to explain the paralysis of the vocal cord. I do believe, however, that tuberculosis may produce this complication. The recent anorexia and weight loss could be explained on the basis of sarcoma of at least four months' duration, but, of course, it could also occur in tuberculosis. The patient concomitantly may have had tuberculosis of the left upper lobe. The mottling of the left lower lobe described in the protocol was confusing, but now that the films have been interpreted, I shall no longer consider it.

I was unable to find a report of osteogenic sarcoma arising in Paget's disease that metastasized to the heart or pericardium, but I assume that such a metastasis could occur. Certainly, cardiac metastases are seen in widespread melanoma and less often from other primary tumors. In these exercises we tend to remember individual cases, and I have seen a case of a colloid adenocarcinoma of the rectum with metastases that in some respects closely resembled this one. When a thoracotomy was performed on that patient a very large ductus lymph node that was associated with paralysis of the left vocal cord was found.

I believe that a sarcoma developed in the right lower end of the humerus, metastasizing to the lung and then to the ductus lymph node.

DR. JOSEPH C. AUB: I should like to look at the x-ray films. There is some periosteal reaction. The thing that puzzles me about this is whether there could have been two lesions. The lumps in the lung are close to the hilar lesion. If this was a metastasis, it ought to have been out in the periphery. This could have been a primary pulmonary lesion, with metastases.

DR. ROGERS: I am sure that it could, and I have no way of deciding whether it was tuberculosis or bronchogenic carcinoma.

DR. AUB: I should not be excited by tuberculosis, but I should be by a primary pulmonary carcinoma with metastases to the bone. I think that your diagnosis may be correct, but I should seriously consider carcinoma. It is embarrassing that no phosphatase determination was done.

DR. CASTLEMAN: A phosphatase determination was done after the operation; the value was only 7.3 units.

DR. AUB: It should have been higher because of the Paget disease.

DR. HANELIN: How often does an osteogenic sarcoma metastasize to the lymph nodes?

DR. CASTLEMAN: Osteogenic sarcoma or any sarcoma only occasionally metastasizes to the regional lymph nodes.

DR. AUB: I shall state that the tumor was primary in the lung.

DR. MILFORD D. SCHULZ: I think one should pay some attention to the paralysis of the recurrent laryngeal nerve. The occurrence of paralysis of either the phrenic or the recurrent laryngeal nerve, even that caused by metastatic tumor in the mediastinum, is more frequent with a primary cancer of the lung.

DR. CASTLEMAN: That is a good point.

DR. HANELIN: I believe that the paralysis of the left vocal cord was noted at fluoroscopy.

CLINICAL DIAGNOSIS

?Osteogenic sarcoma superimposed on Paget's disease.

DR. WILLIAM P. ROGERS, JR.'S, DIAGNOSES

Osteogenic sarcoma of humerus, with metastases to lung and ductus lymph nodes.

Paget's disease of humerus.

ANATOMICAL DIAGNOSES

Bronchogenic carcinoma, with metastases to (bronchial lymph nodes) and humerus.

Paget's disease of humerus.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Joseph S. Barr, who was in charge of the patient, aspirated a fair amount of material from the lytic lesion. Microscopically, this contained islands of epithelial cells, which were definitely carcinomatous. I believe that the primary tumor was in the lung and was an undifferentiated carcinoma, with metastases to the humerus. I think that Dr. Schulz's point — that when there is hoarseness and paralysis there is a primary tumor with the enlarged lymph nodes around it — is a good one. It is rare to see such paralysis with only a metastasis.

Another point that might be mentioned is that when sarcoma develops on Paget's disease the sarcoma is usually composed of spindle-cell fibroblasts; it is rarely osteogenic.

The patient has received 3000 or 4000 r of x-ray therapy to the mediastinum as well as to the humerus. The pain in the arm has been so severe that Dr. Barr is planning to put a cast on the arm. If that does not relieve the pain I think amputation will be necessary.

DR. SCHULZ: He had a pathologic fracture. That is what has caused the trouble.

MASSACHUSETTS PHYSICIANS ART SOCIETY

44. The Fisherman

Exhibited at the American Medical Association, 1955

Oil Painting by

ELIZABETH Z. KLEINMAN, M.D.
Assistant, Department of General Practice, New England Hospital

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

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HOUSE OF DELEGATES

THE following is a tabulation of the more important actions taken by the House of Delegates of the American Medical Association at its meeting in Chicago from June 11 through June 14, 1956. Those interested in details should consult the minutes of the meeting, which will appear in an early issue of the *Journal of the American Medical Association.*

1. The first progress report of the Continuing Committee on Medical Practices, which was established in Boston in December, 1955, was received. The Committee is composed of 3 general practitioners and 2 other physicians appointed by the Speaker of the House.

2. The second progress report of the Commission on Medical Care Plans, which was established in Miami in December, 1954, was received. The Commission has completed the first phase of its assignment involving a study of the nature and methods of operation of the various types of plans through which persons receive the services of physicians, and is now ready to embark upon the second phase, which has to do with the effect of these plans upon the quality and quantity of medical care provided. The third and last phase will involve a study of the legal and ethical status of the arrangements used by the various plans.

3. A report submitted by the Board of Trustees regarding "areas of understanding" between the American Medical Association and the American Legion was approved, but it was recommended that American Medical Association policy concerning care by the Veterans Administration of veterans with nonservice-connected disability be reviewed in terms of the present exceptions of tuberculosis and mental illness since it may be that other types of chronic illness should also be excepted where there is a shortage of civilian facilities to take care of such illnesses.

4. It was urged that constituent state, county and territorial societies and associations be made aware of the implications of Public Law 569, which provides for the care of dependents of military personnel by civilian physicians in civilian facilities under certain circumstances as set forth in the law.

5. The report of the Committee on Medical and Related Facilities regarding private practice by medical-school faculty members was approved.

6. The permanent and total disability feature contained in H. R. 7225, which would amend the Social Security Act, was denounced again.

7. The American Medical Association position that there should be an impartial and thoroughgoing study of the Social Security Act and its implications was reaffirmed.

8. The American Medical Association stand

in favor of a one-time federal grant to medical schools for "bricks and mortar" but not for academic purposes was reaffirmed.

9. The program recommended by the Cooperating Committee on Graduates of Foreign Medical Schools was approved in principle.

10. The report of the Committee to Review the Functions of the Joint Commission on Accreditation of Hospitals was approved.

11. It was recommended that at least one year of rotating internship precede any specialty training.

12. A recodification of the *Principles of Medical Ethics of the American Medical Association* was accepted. Final action will be taken at the next clinical session.

13. The position was taken that the Veterinary Corps of the armed forces should not be abolished.

14. The Council on National Defense was directed to study and report on a plan by which the medical profession can be mobilized to meet the current and future needs for adequate national medical civil defense.

15. The Committee on Traffic Safety was directed to co-operate with other groups looking toward a solution of the problem of traffic deaths and maiming.

16. It was recommended that the general wholesale and resale purchase of Salk antipoliomyelitis vaccine be returned to normal commercial channels.

17. The Sears-Roebuck Foundation was lauded for its financial aid to medical practitioners and the people of this country.

18. The establishment of a committee to study the problems related to the use of radioactive substances was authorized.

19. A progress report from the Law Department on professional liability insurance was accepted.

20. A resolution calling for the consideration of nonscientific problems (economic, social and political) at scientific sessions of the American Medical Association was disapproved on the grounds that these matters come within the purview of the House of Delegates.

21. A proposal that the Board of Trustees establish a rotating scholarship fund for prospective medical students was rejected because the Student American Medical Association had already established such a fund.

22. The Council on Medical Service and the Council on Industrial Health were directed to reconsider the "Guiding Principles for Evaluating Management and Union Health Centers" to determine whether or not they contain wording that could be construed as an abandonment of the principle of free choice of physician.

REGARDING TORNADOES

WORDSWORTH'S winds that will be howling at all hours have come to be recognized as an annually recurring vernal phenomenon, according to a recent release from the Information Service of the Metropolitan Life Insurance Company. Metropolitan statisticians, studying the climatologic data collected by the United States Weather Bureau for the past decade, have found that May, otherwise classified as the month of merriment, has also been the peak month for tornadoes, and in May nearly a quarter of the deaths from this cause have occurred.

During the period studied tornadoes were responsible for a loss of 1766 lives in the United States, and caused injuries to ten times that many persons; however, there has been, in the last forty years, a tendency for the fatalities to diminish decade by decade. Thus, from 1916 to 1925, the toll was 3114; from 1926 to 1935, 2138; and from 1936 to 1945, 1896, contrary to prevalent opinion. More complete and more spectacular news coverage has possibly magnified the toll of tempest and tornado in the public mind.

Despite the occasional unpredictable tornado that strikes east of the Alleghenies, the Central and Southern states are those that most commonly experience these catastrophic disturbances. As evidence, also, that May does not necessarily witness the worst of them is the record series of blasts that devastated the Missouri Valley states on the week end of March 22, 1952, when 208 persons lost their lives. In 1953, in June, a similar series killed 142 persons in Michigan and Ohio, and in the same month the tornado that struck Worcester, Massachusetts, exacted a toll of 88. The largest loss of the decade in a single windstorm was that of 169 lives in Oklahoma and Texas in April, 1947. In May, 1955, 114 persons perished in a veritable explosion of tornadoes that visited Kansas and other prairie states.

Already 1956, the first year of a new decade, according to the current computations of the Metropolitan statisticians, has delivered a sample of its own untoward aerial disturbances. Despite the noted unpredictability of tornadoes, in distinction to the hurricanes that seem now to have made the northeast coast a regular point of call, it is becoming increasingly possible to give advance warnings to communities in their path. It may yet be practical for intrepid observers, like the Duke of Marlborough, to ride in the whirlwind, even if they cannot, like that imperturbable commander, direct the storm.

DISABILITY FREEZE

THE Advisory Committee to the Department of Health, Education and Welfare, responsible for establishing medical standards for the determination of dis-

ability under a recent revision of the Social Security Act, is desirous of having the medical profession informed of its own obligations in the matter.

The so-called disability-freeze provision, enacted in 1954, permits persons with prolonged total disability to have their social-security status "frozen" for the duration of the disability upon acceptance of an application. To have the record so frozen the worker must demonstrate a clear and acceptable social-security status up to the time of the disability and must have a medically determinable physical or mental impairment of at least six months' standing sufficient to keep him from gainful employment, and of permanent or indefinite duration.

The hospital or institution in which the worker has been confined, *or the physician who has treated the applicant and knows his case,* must supply the evidence needed to establish the character of the applicant's disability, its beginning and its prognosis. This information is entered in a medical-report form supplied by the worker and modeled after those used by various life-insurance companies in relation to their disability claims. The worker is himself required to see that medical evidence is submitted and to pay any costs in connection with it.

Final determination of the disability is made by members of a state agency, usually that most concerned with vocational rehabilitation, and each person applying is informed of the rehabilitation services that may be available; at least one member of the determining group is a physician.

The following points have been issued as guides for the collection of evidence and its presentation:

First, include sufficient clinical detail to enable the reviewing team to make a sound determination as to the severity and extent of the patient's current condition;

Second, give enough of the clinical history to provide information as to when the disability began, and when it became so severe as to keep the patient from working;

Third, describe the probable course of the condition from now on, so that a decision can be reached as to whether the impairment is likely to continue indefinitely, or end in death, or whether it is self-limiting, or remediable in the immediate future.

WORLD HEALTH ORGANIZATION — SEVENTH ANNUAL REPORT

Dr. M. G. Candau, director-general of the World Health Organization's, presented to the Ninth World Health Assembly, which opened in Geneva on May 8, a summary of the Organization's seventh full year of activity. During this banner year the Organization achieved a total membership of 85 nations, including associate members, and assisted in the prosecution of over 500 health projects in 108 countries and territories at a cost of $9,500,000.

The Organization, among other activities, started pilot studies to test the success of the home treatment of tuberculosis with the newer drugs, continuing at the same time the BCG campaigns that have resulted in the testing of some 26,000,000 persons and the vaccination of 10,000,000. By the end of the year 50,000,000 persons had been examined for yaws and other treponematoses, and a total of 15,000,000 had been treated with a considerable drop in cost of both examination and treatment.

The atomic program was put on foot, including the training of health workers for atomic installations, the standardizing of radiation units and studies on health problems associated with the location of reactors and the disposal of atomic wastes. Sixty-nine teachers were appointed to 25 schools of nursing, and nearly 1000 fellowships were awarded.

Perhaps the most important event, however, was the inauguration of the program decided on at the 1955 Assembly for the total terrestrial eradication of malaria instead of simply striving for its control. This decision resulted from the knowledge that malaria-bearing mosquitoes are developing resistance to the insecticides in use, indicating that areal attempts at control will eventually prove fruitless. A five-year plan has been drafted, and already, during 1955, teams of experts were at work in 23 areas.

Let parents, at all events, use their common sense, in adapting the occupations they select, to the constitutions of their children; and we shall, not improbably, as one result, see a decrease in that fearful rate of mortality which now attaches to the ghastly Queen *of diseases — Consumption!*
Boston M. & S. J. *July 24, 1856*

CORRESPONDENCE

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held June 7, 1956, it was voted to suspend the registration of Dr. Harold B. Greenfield, 447 Shirley Street, Winthrop, for five months beginning August 1, 1956.

Robert C. Cochrane, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

NONCLINICAL NOTES

APPOINTMENT AT BOSTON UNIVERSITY

Dr. Sydney S. Gellis, physician to the Children's Medical Center, has been appointed professor of pediatrics at Boston University School of Medicine and director of the Department of Pediatrics at the Boston City Hospital. He will continue his appointment at the Medical Center.

NOTICES

ANNOUNCEMENTS

Dr. Ronald E. Finn announces the opening of his office at 5 Bay State Road, Boston, for the practice of internal medicine.

The Health News Institute announces the opening of new offices at 1411 Lincoln Building, 60 East 42nd Street, New York 17, New York.

FIRST INTER-AMERICAN CONFERENCE ON OCCUPATIONAL MEDICINE AND TOXICOLOGY

The University of Miami School of Medicine in joint sponsorship with the University of Havana, Cuba, School of Medicine, will hold the first Inter-American Conference on Occupational Medicine and Toxicology at the University of Miami School of Medicine, Miami, Florida, September 3 through 7.

SOCIETY MEETINGS AND CONFERENCES

JULY 20–AUGUST 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 5–7. First Inter-American Conference on Occupational Medicine and Toxicology. Notice above.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, JULY 26

THURSDAY, JULY 26
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Open Heart Surgery. Drs. Dwight E. Harken and Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JULY 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham. Carney Hospital, Dorchester.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, JULY 28
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, JULY 30
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.

TUESDAY, JULY 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, AUGUST 1
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathologic Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.